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THE BLOOD PICTURE IN PNEUMONIA*

With Special Reference to Pathological Changes in the Neutrophils

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Blood changes in infections, especially pneumonia, have been observed for the past hundred years. The early investigators, working under technical difficulties, arrived at uniform results, namely:

(1) Leukocytosis is present in the majority of pneumonia cases.

(2) Leukopenia often indicates a fatal prognosis.

(3) A possible relationship exists between the number of leukocytes, temperature, and area involved.

(4) In the majority of cases, a transitory rise in the number of leukocytes appears during the early period of crisis, followed by a diminution.

(5) Temperature reaches a normal level several days before the return of leukocytes to normal.

(6) Delayed resolution and complications are accompanied by an increase in the number of leukocytes.

(7) A steady rise in the number of leukocytes prognosticates a fatal ending.

Subsequent investigations were concerned with the variety of cellular reaction as well as with the leukocyte count in pneumonia. Türk,[26] Gaitskell[7] and others observed the following changes:

(1) Marked increase in the number of polymorphonuclear neutrophils; (in one case up to 96.5 per cent).

(2) A diminution in the percentage of lymphocytes.

(3) A disappearance or marked diminution in the eosinophil count.

(4) A diminution in the percentage of polymorphonuclear neutrophils after crisis.

(5) Appearance of myelocytes in many cases, most frequently at the crisis.

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Hickling[10] found a transitory monocytosis after the crisis which bears no relation to prognosis.

Arneth[2] differentiated the polymorphonuclear neutrophil cell, according to the number of lobules in the nucleus, and suggested five divisions and many subdivisions. In cases of acute infection, he noted a marked increase in the number of cells, with fewer lobules in the polymorphonuclear neutrophils, indicating their increase by the term, "shift to the left." Due to the complexity of the Arneth formula, Schilling[25] suggested the following modification: (1) myelocytes (rarely found in normal blood), (2) young (up to 1 per cent), (3) staff or band (4 per cent), and (4) segmented leukocytes (67 per cent). In infections he found a marked increase chiefly in the staff (band) and young forms. Reznikoff[22] in a study of seventy-eight cases of pneumonia found that, in 80 per cent of the patients who died from pneumonia, more than 30 per cent of the cells were immature polymorphonuclear neutrophils, which correspond to the staff (band) form of Schilling, and more than 40 per cent of all polymorphonuclear cells were immature; of those that recovered, 55 per cent showed more than 30 per cent of all cells to be immature, and 48 per cent showed more than 40 per cent of all polymorphonuclears to be immature.

Although the Arneth count has been somewhat modified by Schilling and by Cooke[5] the present tendency is to adopt a still more simplified method, particularly one first proposed by Kothe[12] and emphasized recently by Pons and Krumbhaar,[20] who classified the polymorphonuclear neutrophils into segmented cells (average 70 per cent) and nonsegmented cells (average 4 to 10 per cent). Similarly, Farley, St. Clair and Reisinger[6] classified the polymorphonuclear neutrophil cells into filamentous and nonfilamentous forms. This simpler classification is more readily understood than the more complicated hemograms of Arneth and of Schilling.

PATHOLOGICAL CYTOPLASMIC CHANGES

Important as the number of leukocytes and the differential count may be in determining the severity of the infection, it is, however, not diagnostic, as increases and changes may occur in

conditions other than infection. Certain studies on the toxic changes of the cytoplasm of the polymorphonuclear cells are equally if not more important. Cesaris-Demel[4] described degenerative changes in polymorphonuclear cells in severe infections. Graham[9] called attention to the changes in cytoplasm in severe infections, especially pneumonia, as shown by the diminution of the peroxidase granules. With the improvement of the patient these granules increase to their normal number. Using the ordinary blood stains (Jenner, Wright, Giemsa), Schleip,[24] Türk,[27] Naegeli,[18] and Alder,[1] called attention to the deeply stained basophilic granules in severe infections. These are called toxic granules and are found in segmented as well as in nonsegmented polymorphonuclear neutrophils. Vacuolization is usually seen in segmented forms.

Pelgar[19] called attention to another variety of cytoplasmic degeneration in which there is an absence of both granulation and peroxidase reaction, thus confirming Graham's findings.

Observation of the toxic granules in polymorphonuclear neutrophils is a valuable aid in the diagnosis and prognosis of cases of pneumonia. Pelgar observed the invariable presence of toxic granules in lobar pneumonia; their absence left no doubt as to the diagnosis. He cites an interesting case of so-called sepsis in a man sixty-one years of age whose chest was apparently negative. The blood count was: leukocytes, 33,000; nonsegmented polymorphonuclear neutrophils, 42 per cent; segmented polymorphonuclear neutrophils, 39 per cent; lymphocytes, 15 per cent; monocytes, 4 per cent; neutrophils with large toxic granules, 96 per cent. Pelgar considered the leukocyte count too high for sepsis, believing it to be typical of lobar pneumonia; he suggested the latter diagnosis despite the chest findings, and ventured a fatal prognosis. The signs of pneumonia only appeared three days prior to death. Postmortem examination revealed right upper lobar pneumonia with grey hepatization.

In bronchopneumonia, Pelgar found the toxic granules to be of smaller dimensions. The percentage of cells presenting these cytoplasmic changes was lower than in lobar pneumonia.

Mommsen[15] also demonstrated the constant presence of toxic

granules in lobar pneumonia. He observed a rapid increase in the percentage of cells showing toxic granules; they reached their maximum (100 per cent) a few days after the crisis, and gradually returned to normal by the third or fourth week. When complications arose, particularly empyema, the number of toxic granules remained high (60 to 70 per cent) for weeks.

Gloor[8] observed forty-seven cases of lobar pneumonia and noted the presence of toxic granules in all, but was unable to follow the quantitative variations in the toxic cells.

Mommsen[16,17] reported additional findings on variations in the polymorphonuclear cells with toxic granules in eight cases of lobar pneumonia. Again, he found the maximal curve after the crisis. Even as late as the third week he observed that 30 to 40 per cent of polymorphonuclear cells may show toxic granulation. As the segmented and nonsegmented polymorphonuclear neutrophils usually showed the same percentage of toxic granules, he believed their presence could not be considered as an indication of immaturity of the cell. Furthermore, he believed that toxic granules are the result of physico-chemical alterations and that actual granular formation occurs extravascularly.

Bullowa, Rosenbluth and Merkin[3] examined the blood in 130 cases of pneumonia by means of the supravital technique (Sabin[23]). The cells were found to be motile and, following serum treatment, presented no leukocytic changes before or after chills. The polymorphonuclear count had no relation to the recovery. Vacuolization and non-motility of the polymorphonuclear cells were found with greater frequency in patients who died.

IDENTIFICATION OF TOXIC GRANULES

The toxic changes manifest themselves by anisocytosis of polymorphonuclear neutrophils, slight degenerative alterations in the nucleus, and the presence of basophilic granulation in the cytoplasm (figures 1 and 2). These toxic or degenerative granules are of two kinds, small and large, and stain deeply basophilic with the usual blood stains. The small granules are distributed among the pinkish neutrophilic granules, and are present in milder forms of infection and during the period of convalescence.

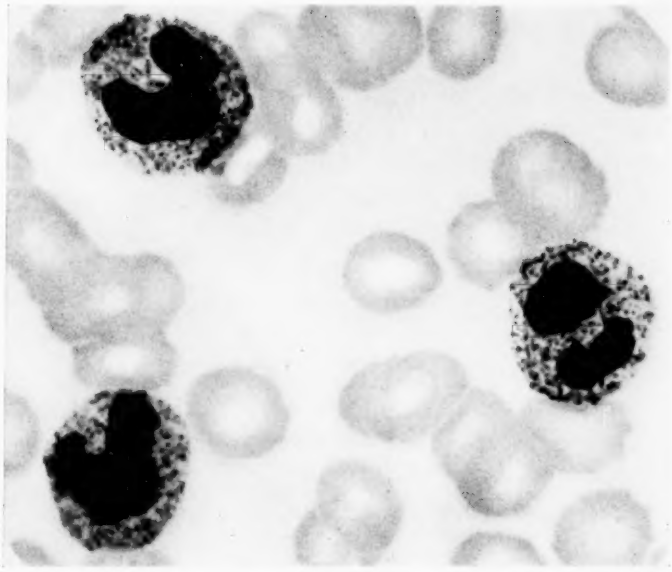

FIG. 1. TUBERCULOUS PLEURISY (CASE 40). NONSEGMENTED POLYMORPHONUCLEAR NEUTROPHILS WITHOUT TOXIC GRANULES (× 1500)

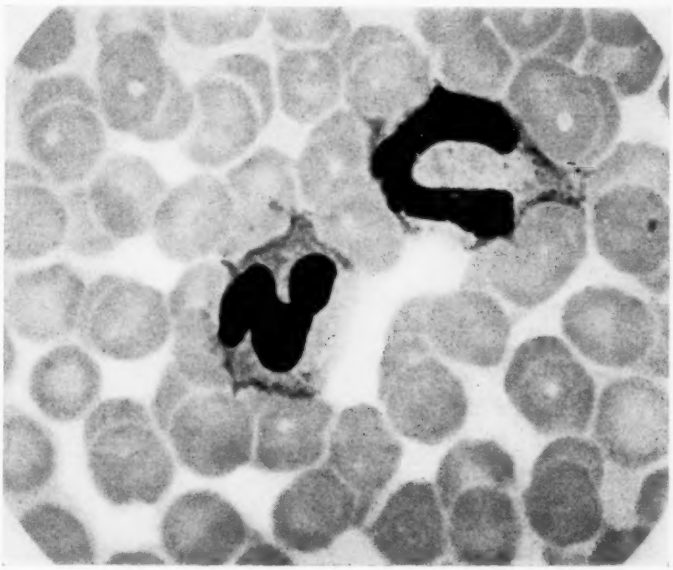

FIG. 2. ACUTE LOBAR PNEUMONIA (JENNER-GIEMSA STAIN) (CASE 14). ONE SEGMENTED AND TWO NONSEGMENTED POLYMORPHONUCLEAR NEUTROPHILS WITH TOXIC GRANULATION (× 1500)

The larger toxic granules appear in cells devoid of pinkish neutrophilic cytoplasm, and are present in severe infections. Lighter bluish cytoplasmic masses may likewise be present in severe infections; these correspond to the Doehle bodies, first described in scarlet fever.

Due to variations in the stains, control smears are important in the differentiation of these granules. Such control smears can be made by using one-half the slide for the patient's blood and the other half for normal blood.

The most practical stain is that of Wright, with the use of a buffer solution (pH 6.4). Best results are obtained, however, with the Jenner-Giemsa stain, using a buffer solution, (pH 6.8 to 7.0). Staining is performed as follows:

(1) Jenner stain (National Aniline & Chemical Company) is used, sufficient to cover the slide for one minute.

(2) Dilute with buffered distilled water (pH 6.8 to 7.0) for three minutes.

(3) Wash off diluted stain with buffered solution.

(4) Cover slide with Giemsa Stain (R. A. L.), diluted with one drop to 1 cc. of buffered distilled water.

(5) Wash and allow to dry in the air.

The buffer solution for the Jenner-Giemsa stain can be prepared by diluting 0.5 cc. to 3.0 cc. of M/15 Na_2HPO_4 to 1000 cc. of distilled water; the amount added varies with the original pH of the distilled water.

For Wright's stain, the buffer solution recommended by McJunkin[14] is preferable. This buffer is prepared by dissolving 6.63 grams of Merck's monopotassium phosphate and 2.56 grams of Merck's anhydrous disodium phosphate in 1 liter of distilled water (add about 1 cc. of chloroform).

A comparative study of the number of polymorphonuclear cells with toxic granules (Figure 2) with the total number of polymorphonuclear cells offers a guide to the progress of infection. The degenerative index may be obtained from this ratio:

$$\frac{\text{number of toxic polymorphonuclear cells}}{\text{total number of polymorphonuclear cells}}$$

A rise in the index to 100 per cent, with the appearance of large toxic granules, indicates a severe or widespread suppurative infection. A gradual or rapid diminution in the index indicates a good prognosis (Kugel and Rosenthal[13]).

Complete blood counts are also made at frequent intervals using a modified hemogram. (See example as illustrated in table 1.)

CASES ILLUSTRATING RECOVERY FROM PNEUMONIA

The following selected cases (table 2) illustrate some of the variations in the blood picture in mild, severe and complicated lobar pneumonia.

Case 10 (Mild type): Patient, aged fourteen years, was admitted to the hospital a year previously for asthma and readmitted with a three-day history of pain in chest, cough, and fever. Signs of lobar pneumonia were present in

TABLE 1

MODIFIED HEMOGRAM

Patient: C. B. (Case 29). Ward: E. Date: 2-13-31.
Diagnosis: Lobar pneumonia.
Hemoglobin: 85 per cent.
Erythrocytes: 4,550,000. Platelets: 760,000. Leukocytes: 31,000.

	TOTAL	NORMAL	TOXIC
	per cent		*per cent*
Differential count:			
Polymorphonuclears, nonsegmented....	43	0	43
Polymorphonuclears, segmented.....	41	0	41
Polymorphonuclears, eosinophile.....	0		
Polymorphonuclears, basophile.....	0		
Lymphocytes.....	12		
Monocytes.....	1		
Other cells:			
Myelocytes.....	3		

Degenerative index: 100.

Clinical data: acute lobar pneumonia thirteenth day of illness. Died on the fourteenth day of illness.

the right, middle and right lower lobes (confirmed by x-ray). The temperature (105°) dropped in four days by crisis.

The blood picture on admission (4th day of illness) showed a moderate leukocytosis and increase of the nonsegmented polymorphonuclear neutrophils (38 per cent), and 51 per cent segmented neutrophils. The degenerative index was 4; this increased daily to 86 after the crisis and returned to normal on the 26th day of illness. A post-critical monocytosis was present in this particular case. The hemoglobin, erythrocytes and blood-platelets were normal.

Case 18 (Severe type): A middle-aged female hospital employee (table 2) with a history of arthritis, complained of chilliness, cough and fever for two days. Dullness was present in the right base posteriorly and in the right

and left apices. X-rays showed bilateral upper lobar pneumonia. The temperature was 103° on admission and dropped by crisis on the 13th day of illness.

Blood Picture (Chart 1): The hemoglobin, erythrocytes and platelets were normal throughout the course. There was a striking leukocytosis of 50,000 to 87,000 before the crisis. The nonsegmented polymorphonuclear neutrophils (71 per cent) fell rapidly to normal by the 17th day while the segmented neutrophils and lymphocytes increased to a normal percentage during the same period. The degenerative index did not run parallel to the nonsegmented cells. It increased rapidly before the crisis to 100 (indicating that 100 per cent

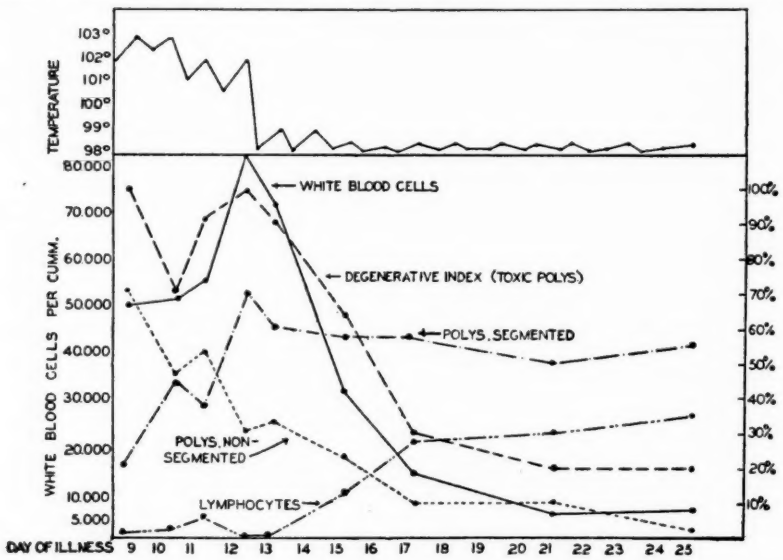

CHART 1. ACUTE LOBAR PNEUMONIA (CASE 18)

of the neutrophils contained toxic granules) and then diminished rapidly to 20 on the 25th day of the illness, when the leukocyte count was 7,900. Notwithstanding the fact that the leukocyte count was normal, evidence of resolution was demonstrated by the presence of toxic cytoplasmic changes in the neutrophils. The myelocytes and monocytes were not increased during the period of observation.

Case 14 (table 2): Pneumonia complicated by empyema. A housewife, aged thirty-one years, developed a cough, bloody sputum, fever, chill, and pain in the right chest five days before admission to the hospital on February 12th (table 2).

The physical examination revealed a lobar pneumonia of the right upper

and lower lobes. Several days later the left lower lobe became involved. The condition had a very stormy course.

The blood changes were typical of lobar pneumonia: moderate leukocytosis (18,000–26,000) and marked increase of the nonsegmented neutrophils to 66

TABLE 2

LOBAR PNEUMONIA—RECOVERED CASES

CASE NUMBER	AGE	DAY OF ILLNESS*	HEMOGLOBIN	LEUKOCYTES	POLYMORPHONUCLEAR NEUTROPHILS		LYMPHOCYTES	MONOCYTES	MYELOCYTES	DEGENERATIVE INDEX	PNEUMOCOCCUS	
					Non-segmented	Segmented					Blood culture	Sputum typing
			per cent		*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*		
1	16	1	80	16,500	16	70	11	3	0	0*	Negative	IV
2	40	2	85	19,600	47	41	10	1	0	57	Type II	
3	22	2	75	15,000	43	48	6	3	0	9	Negative	
4	22	2	85	17,000	56	35	3	1	0	49	Type I	
5	33	2	80	7,200	1	58	28	9	0	34	Negative	IV
6	37	3	75	25,000	47	45	2	4	2	78	Negative	IV
7	30	3	90	20,800	60	23	10	3	4	90	Negative	Negative
8	8	3	72	22,400	56	23	12	8	0	100	Negative	Negative
9	25	4	80	9,500	37	51	4	2	6	72	Type IV	IV
10	14	4	88	16,000	38	51	5	6	0	4	Negative	III
11	35	5	80	8,500	34	38	16	12	0	33	Negative	III
12	22	6	90	13,000	54	25	13	5	0	100	Type I	I
13	27	6	75	22,000	41	46	7	6	0	31	Negative	IV
14	31	6	81	18,500	39	58	2	1	2	92	Negative	II
15	39	7	86	16,600	62	17	17	2	0	98		IV
16	36	7	77	8,000	34	38	21	3	2	80	Negative	III
17	36	8	85	27,000	50	39	4	2	3	75	Negative	Negative
18	40	9	80	51,600	71	21	1	3	2	100	Negative	
19	55	9	78	14,000	64	30	6	0	0	32		
20	44	9	72	23,100	58	29	3	0	0	94	Negative	I
21	23	9	80	11,200	46	24	10	8	10	84		
22	46	12	75	7,500	4	71	12	6	1	86	Negative	I
23	45	14	70	10,000	32	50	13	4	0	72	Negative	Negative
24	17	31	85	12,600	8	51	30	6	0	60	Negative	Negative

* On admission to the hospital.

per cent, occasional myelocytes and the appearance of post-critical monocytosis (13 per cent). The degenerative index was high at first (92) and gradually returned to normal on the 45th day of her illness (March 11th), although there had been an increase in the number of leukocytes to 140,000 (March 9th).

On March 17 (51st day of illness), there was a marked rise in the degenerative index (92). An empyema on the left side was found two days later and thoractomy was performed, 1,000 cc. of pus (subsequently shown pneumococcus III on culture) being evacuated. The patient made an uneventful recovery.

Case 2: Atypical blood findings in a patient with pneumonia, complicated by empyema. A man, aged forty years, addicted to the use of alcohol for twenty years, was admitted with sharp pains in the right chest. Bronchial breathing and egophony were heard at the right base. The roentgen examination confirmed the diagnosis of a right lower lobar pneumonia. The patient was fairly comfortable, the temperature was subfebrile, never above 101. The blood culture was positive for pneumococcus type II. No sputum could be obtained for typing. The blood picture showed a leukocytosis (19,600–31,900) and only a moderately high degenerative index (57). The non-segmented neutrophils were as high as 47 per cent at first (2nd day of illness), but returned to normal by the 13th day. At that time there was still a slight leukocytosis, a normal differential count and absence of toxic granulation. The temperature remained low (100). However, signs in the chest persisted and, later, evidence of a marked accumulation of fluid was found. The right side of the chest was aspirated and the fluid proved to be thick pus. A thoractomy was performed a few days later. The blood picture (table 4) remained normal except for a slight leukocytosis (15,400) and slight increase of the toxic cells (degenerative index (15)).

The deviations from the normal reaction in this patient were: (1) subfebrile course although bacteremia was present, (2) moderate leukocytosis with lower trend in the degenerative index, (3) leukocytosis without increase of the non-segmented polynuclears with the appearance of a severe complication (empyema), (4) absence of toxic granulations in the neutrophils when the empyema was found.

RÉSUMÉ OF OBSERVATIONS ON RECOVERED CASES

Observations on the blood picture during the course of twenty-four cases (table 2) of lobar pneumonia, with recovery disclose the following significant facts:

(1) The hemoglobin, erythrocytes and platelets showed slight variations. The lowest hemoglobin was 70 per cent, the average more than 80 per cent. The blood platelets were uniformly normal. In only two cases were the platelets less than 200,000 per cubic millimeter (140,000 and 150,000).

(2) The leukocytes varied from 7,200 (table 2, case 5) to 51,600 (table 2, case 18). There was no uniformity in their varia-

tions before or after the crisis; there was either an increase or decrease.

The nonsegmented polymorphonuclear neutrophils were increased in all except three cases from 16 to 71 per cent. In three cases of lobar pneumonia, confirmed by x-rays, the nonsegmented polymorphonuclear neutrophils were normal on the patient's admission (table 2, cases 5, 22, 24). In these cases, however, there was a rapid increase before the crisis.

The lymphocytes were markedly diminished. The monocytes were either absent or normal and only slightly increased (8 to 12 per cent) in three cases (table 2, cases 5, 11, 21). A post-critical monocytosis was exceptional.

(3) The degenerative index (the percentage of polymorphonuclear neutrophils with toxic granules) was found to be very high (31 to 100 per cent) with three exceptions: Case 1 represented an atypical one-day pneumonia (Woillez Disease) confirmed by roentgenogram. Some consider this condition a result of pulmonary congestion and not a true pneumonia (Ramond[21]). Case 3 and case 10 (table 2) were mild cases, but the degenerative index rose rapidly to 70 and 86 respectively at the crisis and returned to normal by the end of the third week. The downward trend of the degenerative index is a good prognostic sign.

(4) In patients addicted to alcohol the blood findings were less typical. The degenerative index was comparatively lower. During severe complications, such as empyema, the nonsegmented polymorphonuclear neutrophils and the degenerative index may be normal.

FATAL CASES OF PNEUMONIA (TABLE 3)

The blood changes in fatal pneumonia at the onset showed variations, somewhat similar to those of the recovered cases. A moderately severe anemia was present in three cases only. The leukocytes varied from 5,100 to 36,000; in four cases (table 3, cases 25, 27, 31 and 34) there was a subsequent marked leukopenia which may be considered an unfavorable sign. The degenerative index was invariably 100 during the course of observation, in all but one case. In this patient (table 3, case 34), the pneu-

monia was of a chronic type. The patient was quite toxic and a leukopenic tendency was present, the highest degenerative index being 37. The persistence of the high degenerative index (100) in these cases may be considered a bad prognostic sign, and as such is more reliable than the variations in the nonsegmented polymorphonuclear neutrophils.

TABLE 3

LOBAR PNEUMONIA—FATAL CASES

CASE NUMBER	AGE	DAY OF ILLNESS*	HEMOGLOBIN	LEUKOCYTES	POLYMORPHONUCLEAR NEUTROPHILS		LYMPHOCYTES	MONOCYTES	MYELOCYTES	DEGENERATIVE INDEX	PNEUMOCOCCUS	
					Non-segmented	Segmented					Blood culture	Sputum typing
			per cent		*per cent*	*per cent*	*per cent*	*per cent*	*per cent*			
25	40	3	82	8,400	72	15	4	2	0	100	Negative	
26	45	5	88	20,400	51	43	4	2	0	100		
27	37	7	79	8,000	20	59	18	3	0	100	Type IV	Negative
28	80	7	80	21,800	44	42	13	1	0	100	Type III	Negative
29	45	10	85	31,000	43	41	12	1	3	100		
30	57	11	86	24,000	28	65	6	1	0	100	Negative	I
31	5	12	65	5,100	48	15	15	13	9	100		
32	40	13	55	36,000	55	37	6	1	0	100	Type IV	
33	28	14	85	18,850	26	56	16	2	0	100	Negative	Negative
34	40	14	75	6,100	37	45	16	2	0	47	Negative	IV

* On admission to the hospital.

CASES SIMULATING PNEUMONIA

The constant presence of toxic granulation in the polymorphonuclear neutrophils in pneumonia is an important diagnostic criterion in the differentiation of such cases from those simulating pneumonia. The following case will serve as an example:

Case 40: A man, aged forty-two years, was admitted to the hospital complaining of a severe chill which had lasted for ten minutes, and a cough. His temperature was 103°.

Dullness was present in the right chest posterior to the angle of the scapula. The heart was not displaced. The blood culture was negative. Roentgenogram revealed a shadow to the right of the heart which seemed to be a peri-

mediastinal pleural effusion. The blood examination showed a leukocyte count of 6000 and 31 per cent of nonsegmented neutrophils. During his stay in the hospital, toxic granules were not found (fig. 1) so that pneumonia could be definitely ruled out. Later observations indicated that the patient was suffering from a tuberculous pleural effusion.

The reverse is also important, as seen recently in a child who was brought to the hospital for an appendectomy. There were some abdominal signs, and even slight tenderness in the right lower quadrant. The blood examination revealed the presence of toxic granulations which led to a suspicion of pneumonia. The surgeon was advised to delay operation until a roentgenogram of the chest was done which confirmed the diagnosis of pneumonia.

Other patients were admitted to the hospital with a tentative diagnosis of pneumonia. The absence of the toxic granules for the first few days, or their marked diminution, helped to rule out this particular diagnosis.

Recently, patients have been observed with cardiac decompensation and pulmonary signs. The symptoms as well as the physical signs in the chest may closely resemble pneumonia. The presence of toxic granules is definitely indicative of pneumonia; their absence points to congestion, infarction and other conditions.

DISCUSSION

Several factors must be considered with respect to the blood changes in lobar pneumonia, and their relation to diagnosis and prognosis.

The number of leukocytes showed very marked variation from 4,000 to 144,000, the latter count recently observed in a child. In our series the highest in an adult was 85,000 (chart 1, case 18).

The differential count showed a marked variation in the number of nonsegmented polymorphonuclear neutrophils from 4 to 72 per cent.

Slight secondary anemia was present in about 33 per cent of the cases and more marked anemia in 25 per cent of those that were fatal. These changes are present in other types of infection and are not particularly diagnostic of pneumonia. They seem to indicate the presence of a severe infection.

Cytoplasmic changes with the constant appearance of toxic granules are present in lobar pneumonia and are usually absent in polymorphonuclear cells in other conditions simulating pneumonia, such as pulmonary congestion, infarcts of the lung in cardiac cases, pleurisy with effusion, lung abscess, rheumatic pneumonia, hydrothorax and pulmonary tuberculosis. In pneumonia the toxic granules appear rather early and have been found on the second day in a fairly large number of polymorphonuclear cells. As first pointed out by Pelgar, Hittmaier,[11] Mommsen and Gloor, the appearance of the pathological cytoplasmic changes may be present in all polymorphonuclear cells a few days after the onset of the disease, or they may reach their maximum prior to, or immediately after, the crisis. The percentage of polymorphonuclear cells showing toxic granules, that is, a degenerative index (Kugel and Rosenthal) may be followed throughout the course of pneumonia. This index remains fairly high in some cases for an invariable period, but usually the percentage of cells showing toxic granules rapidly diminishes within twelve to fourteen days after the crisis. However, as late as the third or fourth week, there may be a persistence of smaller granules in polymorphonuclear cells, as reported previously by Mommsen.

The only exception to these results occurred in two patients who were addicted to the use of alcohol. In both, the degenerative index had a tendency to be lower (the highest being 63), returning rapidly to normal as the patient improved.

The factors involved in prognosis are the anemia, the number of leukocytes and the precentage of nonsegmented neutrophils and the degenerative index. The question arises whether the prognosis can be stated definitely from the first examination of the blood. This is sometimes possible when a marked leukopenia is present. Apart from the occurrence of the leukopenia, however, prognosis depends upon the trend of symptoms, the extent of involvement in the lung and the trend of the blood changes.

A severe anemia or a marked increase in the number of nonsegmented cells (above 65 per cent) may presage a fatal outcome. The presence of bacteriemia is not indicative of a bad prognosis, although in the recovered cases here reported, a blood culture was

positive in 20 per cent of the cases, and in the fatal cases, in 33 per cent.

Follow-up of the degenerative index is important in prognosis. A rapidly diminishing degenerative index presages a rapid recovery; gradual diminution of the degenerative index keeps pace with gradual recovery. The persistence of a high degenerative index indicates either a fatal outcome or the presence of complications. A secondary rise in the degenerative index during convalescence is indicative of complications, usually empyema.

CONCLUSIONS

(1) In addition to noting ordinary blood changes, observations on pathological cytoplasmic alterations (toxic granules) are a valuable aid in the diagnosis and prognosis of cases of pneumonia.

(2) Pathological cytoplasmic alterations (toxic granules) are present in all cases of lobar pneumonia, are diminished in bronchopneumonia, and usually are absent in conditions simulating pneumonia.

(3) In recovered cases, the degenerative index—that is, the percentage of cells showing toxic changes—rises rapidly (not infrequently to 100) either prior to, or immediately after, the crisis and persists much longer than the symptoms, that is, to the third or fourth week.

(4) The degenerative index is lower in alcoholic patients suffering from pneumonia.

(5) In fatal pneumonia the degenerative index is frequently 100; its persistence at that level presages a fatal prognosis.

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THE AUTOPSY*

An Outline of the Problem

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In reviewing the literature since 1913 dealing with autopsies, I found 288 articles and editorials in the various American medical and hospital publications. It is possible that some, though probably only very few, were missed. In spite of all this, I feel it may be worth while to review briefly the results of the autopsy movement in this country, and because I believe that the limited success or relative failure, as you wish to call it, is due to a basically wrong conception of the problem involved. To prove that will be the purpose of my presentation.

To begin with, let us look back and review briefly the 288 articles and editorials. The writers are, in the order of frequency, pathologists, physicians, both general practitioners and specialists, hospital superintendents, internes, a few undertakers and one rabbi. They touch upon a variety of aspects of the subject with natural and unavoidable repetitions. The essence of what is expressed and advocated in that veritable library of publications could readily be boiled down to a few brief paragraphs.

The basic question of whether autopsies are at all desirable is quite naturally affirmed by all but one of the contributors, the dissenting voice coming from an anonymous editorial writer of an undertakers' publication in Chicago. One of the medical writers, while advocating autopsies very warmly, is inclined to set an age limit by stating that they ought to be done on persons dying before the age of sixty-five. No reason is given for such a limitation; possibly the author does not care much what happens

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after one is sixty-five. The training of internes, the post-graduate education of the practicing physicians, the advance of medical knowledge, and the establishing of true causes of death and hence placing vital statistics on a sound basis are quoted as the main arguments in favor of autopsies. Having thus established the desirability of autopsies, the authors suggest innumerable schemes which are supposed to enable physicians to obtain permissions for autopsies from the relatives of the deceased. All of those schemes are inspired by the best intentions and when applied are more or less successful. Some of them are unmistakably influenced by the methods of up-to-date salesmanship, as practiced in modern business, but not infrequently the obtaining of an autopsy permit depends on such methods. Those who have personally tried to get permissions for autopsies will probably agree with me. I believe that to this phase, the technic of getting permits for autopsies, hardly anything can be added.

Various religious objections have been thoroughly analyzed and suggestions offered as to how to meet them. A great deal of consideration was given to difficulties arising from lack of coöperation on the part of the undertakers. Their justifiable complaints were presented and the pathologists urged to meet their demands. If we add to the above, suggestions for educational propaganda among physicians as well as among the laity on the value of autopsies we have practically all that is essential which has appeared in the literature on this subject during the last eighteen years.

What are the results? It would be very difficult to estimate, even with an approximate accuracy, the results of this campaign for postmortem examinations. Unfortunately, figures are available only in a few larger cities; in Chicago the Institute of Medicine has published annually, since 1919, a very accurate report. Less accurate data are available for some of the other large cities. There is no doubt that, compared with the conditions which prevailed in 1913, the number of permitted autopsies has greatly increased. Despite the increase, Karsner[1] estimated, in 1927, that less than 0.7 per cent of the country's dead was examined after death. Even if we assume that that figure has since

doubled, it would mean that in more than 98 per cent of deaths in this country there is reason for considerable doubt as to the correctness of the cause of death as given on the official death certificate. Very instructive is the comparison of autopsy percentages for the years 1926 and 1930 in the hospitals approved by the American Medical Association for the training of internes.

An analysis of the figures in the table shows in a rather convincing manner that the increase in the percentages for 1930 in the approved hospitals was the result of the ruling of the American Medical Association. There was no increase in the number of hospitals having 70 per cent or more, or in the whole group of those reporting 50 per cent or less. However in the latter group the number of those reporting 20 to 49 per cent has doubled, while those below 20 per cent have become fewer.

While it is true that autopsies are being performed in non-approved hospitals, as well as in those on the approved list, the efforts are probably greater in those on the approved list and they must be considered as representing the best, most progressive hospitals in the country. There can be no doubt that the increase in the number of autopsies within the groups having less than 50 per cent is a direct result of the pressure by the American Medical Association. Many hospitals are having considerable difficulty to live up to the 15 per cent requirement set by the American Medical Association for hospitals approved for the training of internes.

All this, while it would mean a considerable progress, illustrates that the success is only relative. Furthermore, we are well aware that the efforts expended to achieve the above results are really extraordinary. While in some larger institutions, particularly in teaching hospitals, after the establishment of a routine and organization striving to obtain autopsies, the effort does not seem to be excessive, in smaller, voluntary hospitals a huge amount of energy is being expended. Turner[4] estimated the cost of an autopsy at the Mount Sinai Hospital in New York to be $92.40; he did not include the time and energy of the people engaged in obtaining permissions. It is true that this effort cannot be very easily expressed in dollars and cents. However, the person doing it must be endowed with high grade personality and intelligence,

and his time is valuable. In some hospitals the superintendent, the attending physicians and the internes are spending hours, on occasions, trying to obtain permissions. I am convinced that this effort, expressed in figures, would sometimes come very close to the other expenses involved. Thus, considering all the factors, I believe, and I know that many feel that way, that the result can hardly be called a great success.

Therefore, while we may disagree as to the opinion of how great or how small is the success of the autopsy movement in this country, there is hardly anybody who is optimistic when considering the hospitals as a whole, and not only the large institutions connected with medical schools. Even assuming that the results in hospitals connected with teaching institutions are satisfactory, the fact that they constitute only about 300 of the total of 6719 hospitals does not change the impression that, generally speaking, the number of autopsies is deplorably low.

How are the relatively meager results to be explained? I believe that there are at least two major causes: One of them was discussed in the literature in recent years; the other, the much more important cause, was, to my knowledge, not sufficiently emphasized. I shall begin with the second cause. There is a fundamental error in the general conception of autopsies, particularly as far as the obligations of the medical profession are concerned. I think that it would be best to illustrate this with an example. Suppose that years ago, when, as a result of advanced medical knowledge it became evident that sanitary measures of various kinds, like the dis osal of sewage, disinfection, et cetera, must be employed for the control of epidemics, the task of execution and enforcement had been left entirely to the medical profession without the help of proper laws and of authority of government. What would have been the outcome of such an attempt? What would happen if the physicians would have to get the permission of the people to have them quarantined? Is there a doubt that the movement would have been doomed to dismal failure? To me, there is no difference between the importance of autopsies in all its phases and the problem of sanitation. It is very unfortunate that the medical profession took upon its

own shoulders or had forced upon itself the responsibility of handling that problem.

We are sometimes generous, in fact too generous, in speaking of the conditions in Germany and Austria in that respect, and credit

TABLE 1*

THE EFFECT OF THE MINIMAL AUTOPSY REQUIREMENT OF THE AMERICAN MEDICAL ASSOCIATION UPON THE AUTOPSY PERCENTAGES IN APPROVED HOSPITALS

PERCENTAGE OF AUTOPSIES	NUMBER OF HOSPITALS	
	1926	1930
100–90	3	0
89–80	2	4
79–70	9	10
69–60	13	26
59–50	8	26
49–40	26	59
39–30	42	87
29–20	91	184
19–15	55	143
14–10	107	45
9–5	120	18
4–1	80	2
None	5	1
No record	3	
Not reporting	14	59
Totals.....	578	664
70 or over	14	14
50 or over	35	66
Below 50	526	539
20–49	159	330
5–19	282	206

* Condensed from material contained in the eighth and tenth annual presentations of hospital data by the Council on Medical Education and Hospitals of the American Medical Association. Jour. Am. Med. Assn., **92**: 1043–1127. 1929 and **96**: 1009–1086. 1931.

the medical profession in those countries with the merit of their relatively great success, but we do not realize that there the conditions with regard to autopsies are regulated by laws or by established customs. The medical profession in this country

cannot solve the problem of autopsies any more than it could have been solved by the medical profession of any other country under the same circumstances. No greater handicap could have been put in the way of the movement. I do not know of a more difficult task than is, in some cases, the obtaining of a permission for an autopsy.

In most parts of Germany the custom is that the relatives are notified of the patient's death and have the privilege of protesting against an autopsy during the first twenty-four hours. In Austria, the autopsy in public hospitals is made obligatory by the law. In this country we must approach the relatives for a permission at a most inopportune time. I cannot help feeling, and many who have experienced it will agree with me, that there is a certain cruelty in such an attempt, even when we are dealing with broad-minded people, and particularly so in the case of emotional persons. And who is not emotional at a time when he loses a dear one? It is true that, as conditions are in this country, it almost appears visionary to think of a time when a law will be passed making the performance of autopsies easier; we are afraid to think of the difficulties with which the enforcement of unpopular laws is connected. But, on the other hand, certain sanitary laws are not at all popular and nobody thinks of asking individuals whether they approve of the necessity of being quarantined in the case of epidemic diseases. I used to be very pessimistic in this respect, and I thought that everything else will have to be tried before we think of legislation in regard to autopsies. I believe now that all other attempts will not lead to a great success. It seems to me that a consideration of the development of sanitary laws in this country points toward a possibility of improvement in the autopsy situation.

Is there a doubt in the mind of any one that the autopsy is a public health problem of the greatest importance? The progress of scientific medicine, the question of heredity of diseases are all intimately connected with the autopsy. If a clinical statement as to the cause of death requires the final check-up of an autopsy to be scientifically correct and unassailable, as is generally agreed, then in over 98 per cent of cases the statements as to the causes of

death are not defensible scientifically, and our vital statistics are of very little value. You know how many conclusions of theoretical and practical nature are drawn from vital statistics. To quote only one example: Premiums for life insurance are based on calculations and conclusions derived from the vital statistics. These calculations cannot be correct because the facts on which they are based are not correct.

Now, last but not least, we are coming to the effect of autopsies upon the professional efficiency of the physician. All agree that the training in diagnosing diseases acquired by the medical student in school cannot possibly make him an accomplished diagnostician, and that he has to remain a student of medicine all his life. Everybody admits that the best way for the physician to perfect his diagnostic efficiency is by evaluating his diagnoses and the results of his treatment at the autopsies of those of his patients who had the misfortune to die. The need of experienced physicians is unquestionably of great importance for public health, no less so than medical schools, and still the maintenance of medical schools is not left entirely to the medical profession. What have public health authorities in this country and the government done to secure for the people the undisputed and scientifically established benefits of autopsies? Not one thing. Whatever laws there are, they are directed against and not in favor of autopsies. I do not know exactly, and until now I had neither the time nor the opportunity to study how the sanitary laws in this country were enacted, but I doubt very much whether it was deemed necessary and advisable to educate the masses of people to a point when they themselves demanded that such laws be passed and enforced. The medical profession naturally had to act in an advisory capacity in matters of purely medical nature but was hardly expected to bear the whole brunt of the movement which proved to be of the greatest benefit to humanity. I believe that it will have to be in a similar way that a change in the attitude of the public health authorities will take place relative to autopsies. The sooner the authorities concerned with public health matters realize that, the sooner something will be done. It was simply taken for granted that the problem of autopsies

would be solved exclusively by the medical profession without the help of other agencies and against terrific odds, and the medical profession, already burdened with more difficult tasks than any other, had good-naturedly taken it upon itself. Failure was unavoidable.

I am unfit to make any definite practical suggestions, and have only a few vague ideas on how I visualize the possible future development. The first thing that, in my humble opinion, will have to be done is to have pathologists, statisticians, those specializing in public health matters, and whoever else may feel qualified and inclined prove or disprove that the autopsy is primarily a public health problem concerning the welfare of present and future generations, and that its domain is such that the benefits derived from it cannot be arrived at by any other means. Once this problem is settled, and I believe that it will be settled in the positive sense, then there should not be undue difficulty in changing the entire situation. The National Council on Autopsies now in the process of formation, following a suggestion of the American Hospital Association, may be the logical organization to include into its program the porposals which are here suggested.

I wanted to show in the preceding paragraphs what, in my opinion, was the basic mistake in the concept of autopsies and why the very commendable, though costly, movement to promote autopsies in this country brought only relatively meager results in the last few decades, certainly entirely out of proportion to the amount of effort expended.

I am afraid that objections will be raised that the concept as presented is an impractical dream, that it cannot be realized, and that it may have a depressing and discouraging effect upon the movement, in that it will be employed as an excuse for not attempting to try obtaining autopsies by the means available. Such objections may be justified to some extent but that is no reason for keeping one's eyes closed to the real issue.

I wonder how it can be denied that, as matters stand now, it is generally agreed that the autopsies concern nobody else but the medical profession and the hospitals. Who doubts that by the discarding of such a false and dangerous idea a great deal of good

will ultimately be accomplished? I do not wish to appear visionary and impractical and should not like to be misunderstood. I am fully aware that it may take a long time before anything practical will result. Till then there is a great deal to be done, with the means now on hand, to strive towards an improvement of the prevailing situation.

In this connection I should like to discuss the second major reason for the rather unsatisfactory results of the autopsy movement. The second cause is that the medical profession, while taking upon itself the selling to the public of the idea of autopsies, did not sell it, first of all, to its own members. Thus the fundamental condition was not fulfilled, without which a success could not possibly be expected. Those who doubt the correctness of the last statement are not acquainted with the real situation. Among others, Robertson[3] and Lynch[2], have emphatically expressed this very thought; in fact, it is impossible to improve upon their analyses of this phase. To be even partially successful in the attempt of giving to the people the benefits of autopsies we certainly will have to sell the idea of autopsies, first of all, to our own colleagues, and this duty will have to evolve primarily upon the pathologists of this country. There is one argument in favor of autopsies which, if properly emphasized, will appeal to the medical practitioner more than all the others taken together, and that is that he can never expect to be a good physician unless he follows his patients into the autopsy room. This argument is much more appealing than the importance of autopsies for medical progress, et cetera. It seems strange, but nevertheless true, that a good portion of the medical profession has not come to a full realization of the fact that the autopsy is the most important of all means by which the physician can advance his diagnostic efficiency. This propaganda will not be successful if limited only to theoretical discussions. It is up to the pathologists of this country to prove the advantages of autopsies to the medical practitioners.

Some pathologists will have to lay greater emphasis upon their autopsy work. They will have to perform the autopsy and present the findings in a less detached and academic way, and will have to pay particular attention to the correlation of clinical and

anatomical findings. To do so they will have to acquaint themselves with the clinical point of view; they will have to know very thoroughly the clinical history of the patient, because only then will they be able to point out those changes in which the clinician is particularly interested. One can, after some practice, make the autopsy findings of much greater value to the clinician than is generally believed, and that does not require any concessions so far as scientific accuracy is concerned. The clinician is primarily interested in practical considerations. An autopsy report may be excellent for presentation at a pathological society and at the same time of little value and still less stimulus for a gathering of clinicians. We must emphasize this applied scientific attitude. On the other hand, scientific accuracy should not be sacrificed. The autopsy should not limit itself to the establishing of the cause of death. Such an autopsy satisfies only the diagnostic curiosity of the clinician but does not exhaust the value of the procedure and fulfill its purpose. The quality of the autopsy work will have to be emphasized to a greater extent than it was in the past. Poorly conducted autopsies fail to arouse the interest of the clinicians.

Another point of importance, which concerns mainly the editors of scientific journals, is the fact that not infrequently papers and case reports are being published based upon the study of conditions in which a final check-up by means of an autopsy is not included. In some the conclusions drawn are entirely unjustified without an autopsy. The excuse of failing to obtain an autopsy ought not to be accepted on such occasions. That is where editors could exert a great influence.

More attention will have to be paid to the just grievances of the undertakers. There are a few simple rules to be observed from the time that the patient dies until the body is given over to the undertakers which will be of great help to them and will more than anything else help to gain their coöperation. I should like to suggest that the rules to that effect be printed in our journal and be followed by every pathologist performing an autopsy. A great deal of good can be done by speaking to groups of undertakers, by opening schools of embalming in connection with medical schools,

as was accomplished at the University of Minnesota, where such a school has been functioning since 1914.

The discussions on autopsies at our national gatherings do not necessarily penetrate into the rank and file of the profession. It is necessary for every pathologist to inaugurate discussions in his respective hospital on various phases of autopsies. Much propaganda can be carried on in this way.

There is a conspicuous and ever increasing interest in medical subjects displayed in lay journals of various kinds, if judged by the number of popular medical articles printed in such journals. There is an excellent field for pathologists who have the ability to write in a popular manner, to bring to the attention of the reading public the importance of autopsies for public health.

Another phase which still offers great possibilities is an increase of emphasis on the absolute necessity of autopsies in the curricula of our medical schools. They ought to be used to a greater extent than is done now as a basis for instruction in diagnosis, while at the present time autopsies are used mainly for instruction in morbid anatomy.

CONCLUSIONS

The autopsy has been presented as a public health problem, the solution of which should not be left exclusively to the medical profession. It requires the coöperation of public health authorities.

Until the time when such a program is realized it will be the duty of the pathologist to make the medical profession fully conscious of the value of autopsies.

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THE PATHOLOGIST'S DUTY IN OBTAINING PERMISSION FOR AUTOPSY

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The hospital pathologist who concerns himself only with the performance and diagnoses of such autopsies as are requested is shirking a very important part of his duty. Unless he takes an active part and interest in methods of stimulating an increase in the number of autopsies he hinders the scientific advancement of the staff and institution which he serves. The need and value of a larger percentage of necropsies have been well shown by many leaders in the medical profession. Waite[12] stated that "All roads in medicine lead to, or emanate from, the postmortem table." Christian[5] believed that any hospital service is incomplete without a check-up of the clinical diagnoses in those cases that are fatal and that the autopsy number and percentage is the best single index of the professional efficiency of a hospital. The latter statement is undoubtedly stretching the point a good deal.

A more conservative attitude would be to the effect that the percentage of autopsies is one of the best indices of the scientific attitude of a hospital. Bluestone[2] was more emphatic; "no hospital is larger than its pathological laboratory. . . . . The progressiveness of a hospital is in direct ratio to the laboratory spirit which it maintains." This "laboratory spirit" must essentially emanate from the pathologist, as Bell[1] emphasized, the pathologist must make the physician want to see autopsies on all the clinical cases that die.

Bluestone believed that the medical profession should regard every death from disease as a symbol of their failure to save life. The pathologist therefore, attempts to learn from and help decrease the number of these failures. If the autopsy is regarded as such a valuable adjunct in the study and knowledge of disease

processes and the pathologist is supposedly a leader in this study why, then, should he regard the efforts to increase the number of these studies as a purely administrative and clinical problem and leave that work to others?

The pathologist must incur and maintain the good will and confidence of all members of the hospital staff: internes, house officers, residents, visiting and consulting staff alike. These clinicians are the ones who will, in the end, ask permission for autopsy from the relatives, even beg for it at times. It appears hardly logical to suppose that any human being (and the clinician is no more than human) will force himself to face such situations to supply the necessary work for one whom he dislikes. With an existing feeling of good will the physician will feel a personal interest to obtain this essential examination in every possible case.

The pathologist should encourage the clinical staff to view every patient who is dangerously ill as a possible subject for postmortem examination. Keeping this possibility in mind the attending staff can mold the feelings of the relatives while the patient is still living so that they (the relatives) will feel a return obligation to grant requests that the staff asks of them. There are many excellent papers containing valuable suggestions for use in the development of this "consent psychology" on the part of relatives. It is not the intended scope of this paper to discuss this important phase in gaining permission for autopsies but a partial list of the more important articles is worthy of reference. Bluestone, Bell, Gordon,[6] Tarr,[11] Warwick,[13] Boyd and Gordon,[3] Parkhurst[10] and Charache[4] have written papers which are recommended to pathologists and clinicians alike for their valuable aids and suggestions. Religious misbeliefs form an important subject in the refusal of permission for autopsy and such objections are cited by Joslin,[8] Gottlieb[7] and Lauterbach.[9]

Clinico-pathological conferences are an excellent method of stimulating the staff to want to see autopsies and to verify the clinical diagnosis on their patients that die. The pathologist should urge them. This institution holds such a conference each month. At the meeting, one case is presented as a problem by the staff who treated the patient. The remainder of the staff

discusses it from the psychiatric, medical and therapeutic viewpoints and the pathologist engages in the discussion of the necropsy findings.

The relatives in nearly every instance, wish to share in the knowledge of the findings and diagnoses of the examination. It is much easier to obtain a request for an examination from individuals who know beforehand that they will be told of the causes of death. Without this the relatives consent only on the argument of "assisting science" which is a very impersonal and lofty one. Doctor William A. Bryan, Superintendent of this institution, devised and routinely sends a form letter to the relative of every patient on whom necropsy has been performed. A typical letter of this type is:

My dear Mrs. Doe:

I am writing to give you the results of the examination which you so kindly permitted us to make, following the death of your husband, John Doe.

We find that his death was caused by pneumonia. He had a chronic kidney disease and ulcer of the stomach. There was a marked degree of hardening of the arteries of the brain which accounted in some measure for his mental symptoms.

May I express my personal sympathy to you at this time and assure you that the hospital did everything possible to make your husband comfortable during his last illness. He suffered very little and his death was peaceful. The rites of the Church were administered to him by our Catholic Chaplain.

If the hospital can be of any further service to you at any time, please do not hesitate to call on us.

It is to be noted that this letter is worded in the very simplest of English terms. The relatives receiving such a letter must feel that they too have gained by granting permission. The pathologist would do well to take on such a duty personally, if it is not already done by the institution.

The pathologist must coöperate with the undertakers who receive the bodies on which autopsies have been done. The undertakers compete by making the corpse attractive in the least possible time. It takes two or three extra hours' work to accomplish this even under the best of conditions. When this work is increased because of carelessness on the part of the one who performed the autopsy, is it small wonder that the members

of their profession are antagonistic towards autopsies in general? This ill-feeling can be remedied and has been remedied to some extent in this community.

The pathologist might interview the morticians of his community. Doctors Bryan and Flower have been responsible, in a large measure, for the existing good feeling between the local undertakers and this institution. These doctors interviewed the group and asked for their reasons for previous antagonistic attitudes. To change this attitude it is important that we follow out the suggestions that the undertakers made. By so doing, it must interest them in our getting and doing autopsies. In this connection, Doctor Bryan uses another type of form letter which he sends to every undertaker who collects a corpse on which autopsy has been performed in this institution:

Dear Sir:

This hospital is endeavoring to give the best and most efficient service to the members of your profession. We are anxious to render every assistance to visiting morticians, and in order to check up our methods, I am writing to ask if everything was satisfactory in the case of Jane Doe, delivered to your firm May 17, 1932. An answer to the following questions will be appreciated.

Did you receive prompt and courteous attention when you called for the body?

Was the body in good condition?

Have you any suggestions to offer that will facilitate your work in any way?

Are our autopsied bodies in good condition, and can you suggest any way in which we can improve our autopsy methods?

We desire to coöperate with you in every way, and if anything occurs in the future that requires correction, please inform me at the earliest opportunity.

We have received many interesting and valuable suggestions from these letters. We had one of the group demonstrate his method of embalming an autopsied body in our laboratory so that we could visualize his difficulties and improve our technic to make those difficulties less troublesome. In return we have been more than compensated by the mortician's change of attitude and aid in advising their clients to allow us to perform post-mortem examinations.

The results of these conferences with the undertakers have elicited the following points as essential in every necropsy and

are deemed worthy of elaboration. These routine procedures take very little extra time.

WRIST AND CHIN TIES

The corpse should not have any wrist or chin ties. When the body is "laid-out" on the wards by the nurses it has been their custom to secure the two wrists by tying with a wide bandage. They also close the mouth by bandaging the lower jaw tightly to the head. As rigor mortis sets in, these ties leave visible marks on the corpse at the funeral that are particularly unsightly. Undertakers on the whole prefer that these ties be omitted. The sleeves may be pinned to the body of the shroud to prevent the slipping of the arms. If the chin does sag they much prefer to wire the upper and lower jaws together from the inside of the mouth.

TRUNK

The "Y" incision is used on all trunks, male or female alike. Starting at both acromioclavicular junctions the incisions are extended downward and towards the anterior medial line, meeting at the xyphoid process. The incision is then extended downward in the midline of the abdomen. This method hides any incision marks at the funeral. The wide thorax incision allows the subcutaneous exposure of all the neck tissues (we remove the larynx in every case) and does not distort it even when a low-necked gown is used to dress the corpse. In those cases where the autopsy is limited to the thorax alone the "V" incision is used identically with the upper half of the "Y." In autopsies limited to the abdomen, the inverted "V" incision is used beginning at the xyphoid and extending to the anterior-superior spines of the ilia. This affords an excellent exposure of the abdominal cavity.

All organs are removed and never replaced within the body cavity. Their remnants are burned in the hospital incinerator. If an organ is allowed to remain within the body, once its blood supply is severed which renders embalming of that particular organ impossible, it will putrefy and give off a very offensive odor. Therefore, the undertaker must do what the pathologist carelessly failed to do.

The feces are milked upward in the tract starting from the rectum so that there will be no remaining stools in the colonic stump that is allowed to remain in the body. The stump of the rectal colon is tied at its severed end. The severed end of the vagina is likewise treated after the removal of the uterus.

The remaining stumps of vessels are tied.* The stumps are left sufficiently

* Since writing, the author attended the last convention of the New England Funeral Directors Association. In their unanimous opinion the veins should be left open for free drainage during the process of embalming; only the arteries should be tied.

long (both vessels and twine) so that they may be easily found by the mortician in case he wishes them. The right innominate, left common carotid, and left subclavian arteries are tied in the thorax. The beginning of the two common iliac arteries are likewise treated in the pelvis and the corresponding veins of these vessels are included in the ties. On partial autopsies, if only a portion of the trunk organs are removed, the cut ends of the vessels must be tied.

The empty cavities are sponged and wiped absolutely dry. If this is not done the fluid will soon become odoriferous. The incision of the trunk should be sutured in the same manner as noted above heeding the same precautions.

HEAD

The scalp incision should start just back of the external ear, in the posterior external ear-fold. It is carried on top of the head, well back from the vertex, so that it will not show at the funeral. In case of bald heads the incision is kept within the hairy fringe which is usually present around the occipital portion of the scalp. In this instance the scalp will strip over the face if the ends of the incision are carried downward keeping within the posterior ear-fold. Incisions outside of this ear-fold will show their suture marks at the funeral.

When the brain is being removed the stumps of the two vertebral and internal carotid-middle cerebral arteries are left as long as possible. They are sealed securely by tying with suture material. The corresponding optic nerves may be included in the tie of the internal carotid arteries to give body to the walls of the vessels. The pituitary body may be removed without mutilating the stumps. These ties in themselves are usually sufficient to withstand the force of the embalming fluid except if the vessels are sclerotic and brittle. It is well, therefore, after the cavity is sponged and wiped dry to reinforce the ties by filling the lower cavity with plaster of Paris. It is extremely disagreeable to have bloody-embalming fluid stain the pillow of the casket at a funeral because vessels leak and the fluid seeps through the sutured scalp. Plaster of Paris in itself will not prevent such leaks.†

The upper and lower temporal edges of the cranium must be wired on either side to prevent the upper portion from slipping and showing distortion of the head at the funeral. We use an ordinary small bore, carpenter's bitt and number 18 copper wire.

SPINAL COLUMN

The removal of a portion of the spinal column and cord presents a difficult problem on account of its location as the body lies on its back. Ordinarily this procedure allows fluid to seep through the sutured incision and will stain the

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† The funeral directors also disapproved of the use of plaster of paris inasmuch as it may prove to be a nuisance if they should desire to remove it. This procedure would better be left out.

casket lining and clothes, a mishap which is particularly annoying. After the removal of the cord all of the severed vessels are sought and individually tied. The bone fragments are not replaced. The cavity is sponged and wiped dry. The skin incision must be carefully sutured. This technic results in a dry back.

SUTURE AND TIE MATERIAL

A very important point from the mortician's point of view is the suture material. It must not break or it will either allow distortion of the skin of the body or seepage of body fluids and stain the lining of the casket or both. We use Belfast cord which is a starched white cord of very satisfactory strength. The sutures must be close enough to prevent seepage of fluid from the edges of the incisions. We use the baseball stich, each stich not more than one-half inch away from its fellow above or below and keeping the string taut results in waterproof-sutured incisions. Particular care must be used to make the incisions absolutely leak-proof in the head and back.

The skin of a body on which autopsy has been done is next washed and wiped clean and dry. At this time the sutured incisions should be closely scrutinized for leaks. If any does occur it can be stopped by close sutures.

The shroud should be clean and dry. No one cares to handle soiled clothing and the undertaker is no exception. At the time the undertaker calls for the body someone conversant with the extent of the autopsy should verbally inform him of it and the vessels that remain tied. If this is not practicable, in those instances in which bodies are called for out of usual hours, a slip of paper containing the necessary information may be left with the body.

The pathologist should never keep the undertaker waiting for a body. At the time the permission is obtained the relatives are asked the name and address of the undertaker who is to call for the body or if they have not as yet decided upon one, they are asked to have the man they select call to make a definite appointment at which time he may receive the body. Once the appointment is made, an hour being added on to the estimated time for completing the autopsy and preparing the body, the body should be ready for delivery before the arrival of the hearse.

The undertaker has just as much right to call for a body at midnight, providing he has the necessary permits, as during the day. Any delay that the institution may cause by opposing such a right will result only in antagonism and defeat the purpose of increasing the percentage of autopsies.

It is justifiable to ask if the results of such an elaborate and extensive procedure has any compensation. One's answer can-

not be more forceful than the actual results. Our present methods in coöperating with the undertakers were started during the early part of 1931. A comparison between the results in the years 1930 and 1932, inclusive, is given in table 1. It is also worthy of note that since the onset of using this procedure up to the present time more than 180 autopsies have been performed with but one case in which it was granted with limitations as to the extent of the examination.

These methods really add very little extra work as far as the pathologist himself is concerned. A well trained assistant can open the calvarium, remove the brain, split the spinal column, tie the cut vessels and suture the skin while the pathologist is removing, describing and sectioning the organs. The entire procedure has taken us but two hours in our speediest work from start to finish including the weighing and measuring of every organ.

TABLE 1

SUMMARY OF AUTOPSY STATISTICS SHOWING INCREASE IN AUTOPSIES PERFORMED

	1930	1931	1932*
Number patients died	227	220	108
Number autopsies performed	75	116	76
Per cent autopsies performed	33.0	52.7	70.9

* This includes the first five months only.

SUMMARY

Pathologists are urged to take an active part in order to increase the number of postmortem examinations in the institutions which they serve.

Periodic clinico-pathological conferences will stimulate the staff to want to see autopsies performed on the patients who die.

Relatives should, if they so desire, be informed of the results of the postmortem findings. The pathologist must be willing to take on such a duty.

Pathologists must give careful attention to the care of bodies on which autopsies have been performed following the sugges-

tions of the local undertakers. The technic used must be one that aids the embalmer in every detail.

Close coöperation between the pathologist and the undertakers will result in their help rather than antagonism.

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PRIMARY TUMORS OF THE LIVER*

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The main purpose of this paper is to discuss the pathology of primary hepatic tumors and to report eight cases of primary carcinoma of the liver encountered in 1087 necropsies at Detroit Receiving Hospital during the thirty-four months between March 28, 1929, and January 20, 1932. This constitutes an incidence of 0.74 per cent of all autopsies and 8.4 per cent of all carcinomas encountered at autopsy. To this will be added a report of two secondary neoplasms of the liver which possessed features in common with primary tumors of this organ and presented a problem in differential diagnosis. No attempt will be made here to review completely the subject of primary hepatic neoplasms or to collect all of the reported cases. The reader is referred to the articles of Wegelin,[27] Castle,[4] Griffith,[13] Wollstein and Mixsell[30] and Dansie,[7] dealing with primary carcinoma of the liver in children.

The liver may be the site of many rare neoplasms such as cystadenoma, sarcoma, endothelioma, hypernephroma, but those most frequently encountered are of epithelial origin and in the experience of most authors the majority are derived from or resemble liver cells (solid parenchymatous tumors or hepatomas) while the remainder appear to be related to bile duct epithelium (glandular type or cholangioma). Jaffé[16] stated that only forty-eight cases of unquestionable primary sarcoma of the liver had been reported. It is more than possible that many of these primary sarcomas were actually of epithelial origin.

Kelsch and Kiener[18] in 1876 reported two cases of primary carcinoma of the liver and were able to find only one other positive

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case. Sabourin[23] in 1881 added four cases. Hanot and Gilbert[14] in 1888 discussed primary carcinoma of the liver under the separate headings of pathological anatomy, etiology, histogenesis and pathogenesis, symptomatology, diagnosis and treatment including twenty-four in part unpublished observations on this subject. In 1901, Eggel[8] collected 163 cases and added one of his own; of these 163 cases only 117 had been studied microscopically. Wegelin reported eight cases from the Bern Pathological Institute. Ribbert[21] added a valuable contribution.

INCIDENCE

While primary carcinoma of the liver is a lesion infrequently encountered it can by no means be considered rare. It is sometimes difficult to judge whether this lesion is extremely rare or relatively common because its incidence appears to vary greatly in different geographical areas. Clawson and Cabot[5] reported the only case seen in 5100 necropsies at the University of Minnesota. Winternitz[29] found three cases in 3700 autopsies at Johns Hopkins Hospital up to 1916 which constituted an incidence of 0.028 per cent of all postmortem examinations. Heller (quoted by Ascoli[2]) found primary hepatic tumors in only 0.02 per cent of all patients at the Leipzig Clinic and all of these were diagnosed sarcoma. In 1924, Fried[10] reported five of these tumors, one of which was the only case which had been found at autopsy at the Harvard Medical School up to that time.

The other extreme is found in the written reports of other observers. Smith[24] reported twelve cases of primary carcinoma of the liver (nine hepatomas and three cholangiomas) collected during one year in the Philippine Islands in 872 consecutive autopsies, an incidence of 1.4 per cent, or 17 per cent of all cases of malignancy found at autopsy during that time. Strong and Pitts[25] collected nine cases in eight years (1920 to 1927) at the Vancouver General Hospital in 1024 autopsies (0.87 per cent). Eight of these nine patients were Chinese, making the autopsy incidence 0.11 per cent in whites and 6.9 per cent in Chinese. Pirie[20] at the South African Institute for Medical Research, in the nine years from 1912 on, found that in the routine examination

of 3900 tissue specimens a diagnosis of primary carcinoma of the liver had been made in fifty-two cases, thirty-six of which appeared to him authentic; and that it was the commonest tumor in African natives, a race in which malignant disease is exceptionally rare.

An average incidence is recorded in the reports of others such as Allbutt and Rolleston[1] who found twenty-four cases in 18,500 autopsies (0.12 per cent); Goldzieher and Bokay,[12] eighteen in 6000 autopsies (.03 per cent); Rowen and Mallory,[22] nine in 6506 (0.13 per cent); Wheeler,[28] 15 in 5233 (0.28 per cent); Counseller and McIndoe,[6] eight in 5796 (0.14 per cent) and von Glahn and Lamb,[11] six in 1800 cases (0.33 per cent). The average of all reports would be about 0.2 per cent.

CASE REPORTS

*Six hepatomas**

Case 1. A white male, sixty-five years of age, was admitted March 23, 1929 complaining of colicky pain in the upper right quadrant radiating to right shoulder for nine months and abdominal distention for three months associated with intensive jaundice and a twenty-five pound loss of weight. He had drunk two quarts of beer daily and whisky occasionally for fifty years. Hemoglobin was 24 per cent. Kahn and Kolmer tests were negative. Death occurred on March 28, 1929. Necropsy showed that the liver weighed 2100 grams and contained numerous new growth areas which in some portions had coalesced to form larger multinodular masses. The surface was nodular; the liver parenchyma was very hard and offered resistance to cutting. This is the only case in this series in which cirrhosis was present (figs. 1 to 4). The diagnosis was hepatoma with cirrhosis.

Case 2. A white male, aged fifty-two years, entered October 9, 1930 complaining of abdominal pain without jaundice. There was a typical history

* Since this paper was read the author has encountered at autopsy three additional cases of hepatoma, one of which was associated with portal cirrhosis. One of the remaining two was an incidental finding, represented a very early stage, and consisted of a diffuse distribution of many minute nodules, supporting, it would seem, the multicentric theory of origin.

These cases increase the autopsy incidence to 0.85 per cent, change the ratio of hepatomas to cholangiomas to nine to two and revise the incidence of cirrhosis associated with hepatoma to two in nine cases and with all cases of primary carcinoma of the liver in this series to two in eleven.

FIG. 1. TYPICAL SPECIMEN OF HEPATOMA WITH CIRRHOSIS

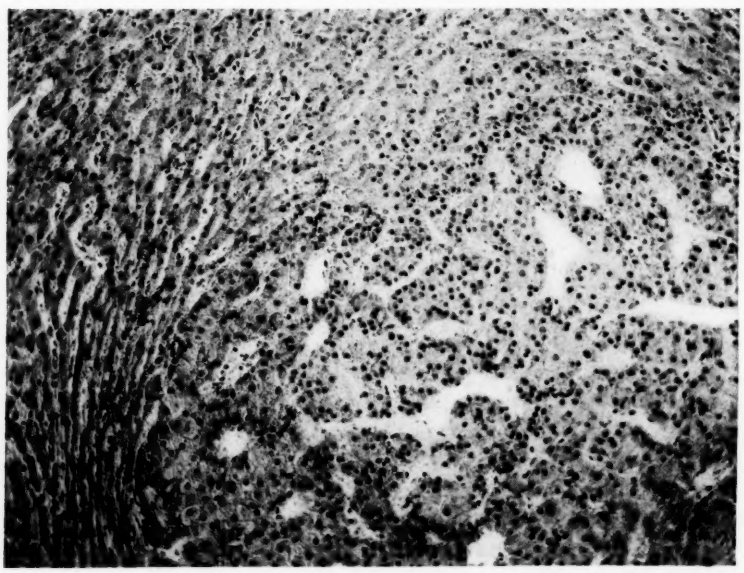

FIG. 2. APPARENT TRANSITION FROM NORMAL LIVER CELLS TO NEW GROWTH TISSUE

Note preservation of typical liver vascularity in carcinoma tissue

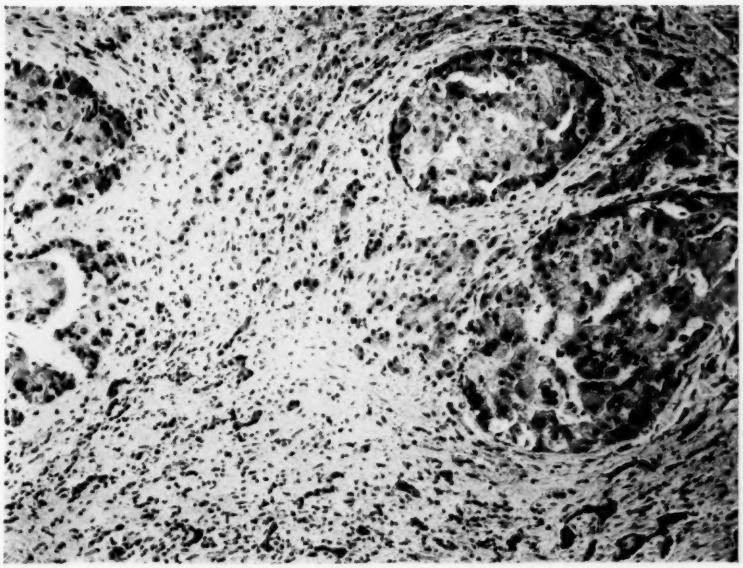

FIG. 3. SMALL NEOPLASTIC AREAS, SOME INTRAVASCULAR, IN AN AREA OF CIRRHOSIS

This picture suggests that these areas of carcinoma were in the beginning simple nodular hyperplasia.

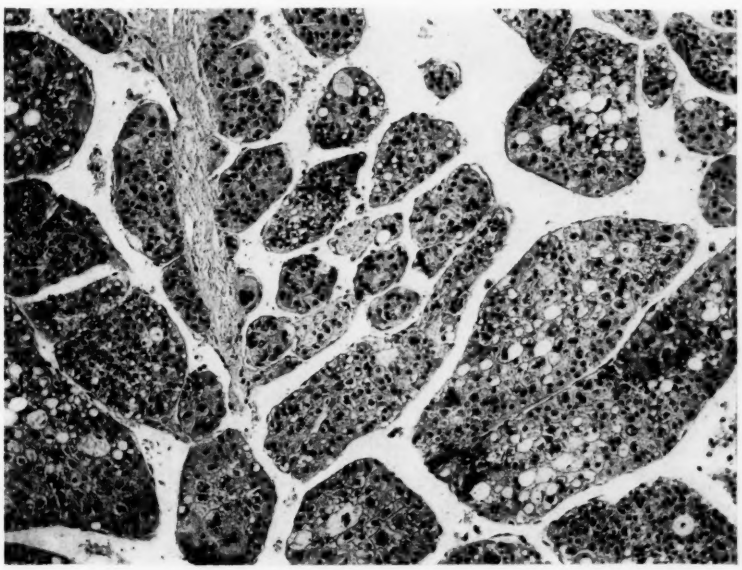

FIG. 4. PAPILLARY AND FATTY DEGENERATION IN HEPATOMA

This tissue is undergoing the same type of degeneration commonly observed in liver parenchyma.

of peptic ulcer or gall bladder disease for the past six years. Laparotomy was performed. Death occurred five days later on October 22, 1930. Necropsy showed that the liver weighed 3800 grams and was diffusely mottled throughout by white and yellow nodules varying in size from 1 to 3 mm. There was metastasis to both lungs, to peribronchial, anterior mediastinal and retroperitoneal lymph nodes and to the pancreas. The diagnosis was multiple hepatoma metastasizing to lungs, mediastinal and regional lymph nodes and pancreas.

Case 3. A forty-six year old white male was admitted on July 27, 1931 complaining of a mass in abdomen, dyspnoea, weakness, jaundice, loss of weight and vomiting for six months. The patient was severely anemic and gave a definite history of alcoholism. Icterus index was 15. Death occurred August 15, 1931. At necropsy the abdomen contained bloody fluid. The liver weighed 5300 grams and contained numerous tumor masses throughout. There was also a large mass of new growth tissue, 15 cm. in diameter, attached to the spleen and producing pressure on the diaphragm and on the cardiac end of the stomach. Thoracic and abdominal cavities were otherwise normal. The diagnosis was multiple hematoma metastasizing to the spleen.

Case 4. A white female, aged sixty-three, was admitted on November 2, 1931 complaining of vaginal hemorrhage. She insisted that she had had no symptoms previous to this acute attack. The abdominal wall was thin. The liver extended two finger breadths below the costal margin and contained a definite palpable hard mass above and to either side of the umbilicus. The patient expired November 3, 1931. Necropsy showed that the vaginal hemorrhage had been caused by a submucous myoma of the uterus. The liver was enlarged and contained numerous masses, the largest of which was 2 cm. in diameter. Metastasis had occurred only to the regional lymph nodes. Diagnosis was multiple hepatoma with metastasis to regional lymph nodes.

Case 5. A white male, aged seventy, came to the hospital because of painful enlargement of the abdomen, the presence of a mass in the upper abdomen, a thirty-pound loss of weight, vomiting and weakness. He was well until six weeks prior to admission. A mass about the size of a grapefruit, apparently continuous with the liver, could be palpated. The mass was extremely painful. Icterus index was 10. Blood count showed 120,000 leukocytes with 83 per cent polymorphonuclears. Death occurred December 14, 1931. Necropsy showed that in the medial portion of the right lobe there was a spherical mass 17 cm. in diameter, bulging the capsule anteriorly and extensively invading the overlying omentum. The central portion of the mass was extensively necrotic. Diagnosis was solitary hepatoma. There were no metastases.

Case 6. A sixty-two year old white male, entered November 6, 1931. Three weeks after recovery from an attack of pneumonia he became jaundiced. The jaundice deepened. There was ascites. The liver was smooth to palpation and extended two finger breadths below the costal margin. He had a moderately severe secondary anemia. Icterus index was 40. He had been a saloon keeper before prohibition. Death occurred January 20, 1932. At necropsy a large amount of clear fluid was found in the abdominal cavity. There were innumerable small new growth nodules throughout the liver with metastasis to the coeliac nodes and the capsule and lymphatics of the pancreas. Diagnosis was multiple hepatoma with metastasis to regional nodes and pancreas.

Two cholangiomas

Case 1. A colored male, forty-four years of age, was admitted April 14, 1929. There had been swelling of lower extremities, dyspnoea, pain in back and cough for one year. Spinal fluid and blood Wassermann were negative. Death occurred June 6, 1929. At necropsy the liver weighed 5800 grams. Throughout both lobes there were tumor masses, the largest of which measured 15 cm. in diameter. The larger masses were fluctuant. The only evidence of metastasis was a nodule 1 cm. in diameter in the wall of the right auricle slightly above the tricuspid valve. (For microscopical picture see Fig. 5.) The diagnosis was cholangioma metastasizing to the heart.

Case 2. A white male, sixty-two years of age, entered the hospital on March 21, 1931, with a diagnosis of chronic alcoholism. He appeared anemic but not jaundiced. The liver in the midline extended to within two finger breadths of the umbilicus and then curved downward almost to the iliac crest. He was semicomatose and expired on March 24, 1931. At necropsy the liver weighed 3000 grams and contained numerous fairly large tumor masses, the maximum diameter of which was 3.5 cm., and also a finer, smaller and more diffuse new growth infiltration. The microscopical picture was similar to Fig. 5. The diagnosis was cholangioma without metastases.

Two melanomas

Case 1. A white male, fifty-two years of age, was admitted November 16, 1927. The symptoms were referable to the urinary tract. He had had a mole removed from his back one year before. Death occurred November 29, 1927. Necropsy showed that death was apparently due to urinary obstruction produced by prostatic hypertrophy. The liver was slightly enlarged and contained numerous pigmented new growth nodules. Microscopically the cells were spherical, polyhedral and spindle-shaped. The intracellular pigmentation was light. The liver was the only organ involved. The diagnosis was melanoma of the liver probably primary in previously excised mole.

Case 2. A fifty-five year old white male entered September 15, 1930, complaining of severe abdominal pain, distention, and constipation. There was no history of nausea, vomiting or jaundice. It was thought that his abdomen contained fluid. Icterus index was 15. Three years before his left eye had been injured and became sightless. Death occurred September 29, 1930. At necropsy the liver weighed 9000 grams, was almost black in color and was diffusely speckled with white nodules from 2 to 15 mm. in diameter. No other organs were involved except the left eye which was atrophic and collapsed and

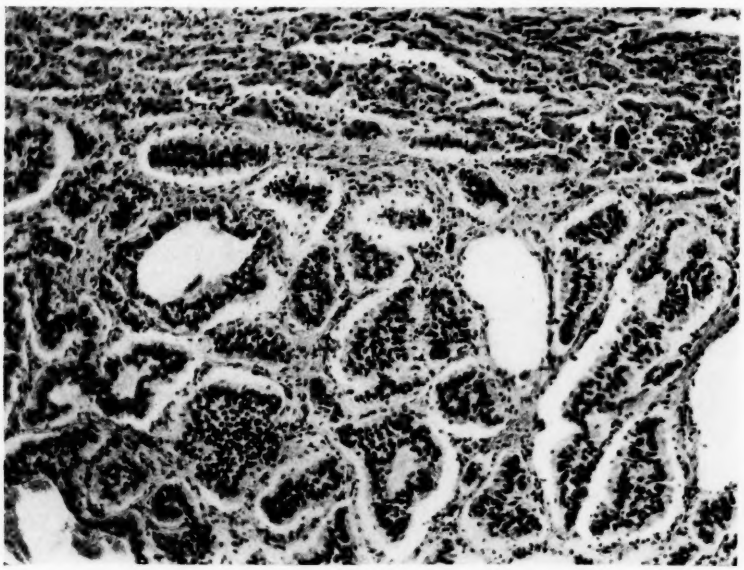

FIG. 5. TYPICAL CHOLANGIOMA

Metastasis in this case consisted of a solitary nodule in the right auricle of the heart.

contained a melanoma of the choroid 5 mm. in diameter. The cells were nearly all spindle-shaped and heavily pigmented. Diagnosis; Melanoma of the choroid with extensive metastasis to the liver.

DISCUSSION

Primary hepatic tumors have always held the interest of the pathologist because of their rareness and because of the many controversial points which the subject precipitates. Discussion in the past has dealt with the following phases: (1) the com-

parative rareness of the lesion; (2) the source of the new growth cells and the incidence of two principal microscopic types; (3) the relationship of adenomas and carcinomas; (4) the gross classification of these tumors; (5) the unicentric or multicentric origin and whether there is transition from normal liver cells to new growth cells; (6) the frequency of cirrhosis as an associated lesion and its rôle as an etiological factor; (7) the part played by chronic hepatic disease such as parasitic infections and chemical damage in the origin of primary malignancy; (8) the comparative infrequency of metastasis.

It is quite generally agreed that hepatoma is more common than cholangioma. Eggel found that ninety-three out of 106 cases were of the liver-cell type. Yamagiwa's[31] ratio was twenty-seven to fifteen; Rowen and Mallory found seven hepatomas out of nine cases; Winternitz and Muir's[19] cases were all of the liver-cell type. Goldzieher and Bokay found fourteen hepatomas and seven cholangiomas. Nine of Smith's twelve cases were hepatomas. Strong and Pitts found only three cholangiomas in nine cases. In Pirie's thirty-six cases, twenty-eight were diagnosed hepatoma, three cholangiomas and five mixed tumor. Ascoli, in a recent article, had collected in eight and one-half years sixteen cases in his own material of which nine were microscopically malignant (autopsy and biopsy at operation). Of these nine cases two were diagnosed cylinder cell epithelioma, one solid carcinoma, two fusocellular sarcoma, two cholangiocellular sarcoma, one cancer cirrhosis, and one primary central sarcoma composed of round and spindle cells. The case of central sarcoma consisted of a solitary tumor the size of an adult's head. In two cases there were massive tumors with smaller nodules scattered throughout the liver. Advanced cirrhosis was associated with one case and mild cirrhosis with another. In spite of the diagnoses given, six of the cases were probably hepatomas and two were cholangiomas. The same author also reported a primary melanoma of the liver. Exceptions to the predominance of the liver-cell group were reported by Fried who made a diagnosis of cholangioma in four of his five cases, and Karsner[17] reported nine cases, five of which were cholangiomas. The doubt concerning

the relationship of bile duct and hepatic cells, the possibility of transition from one to the other, and the apparent common ancestry of these cells might lead one to think that the classification of these carcinomas was a matter of minor importance and perhaps over-discussed. The clinical and pathological similarity of these two tumors might argue for a single diagnosis for the two epithelial types, and there can be no great objection to calling them all hepatomas.

The division of epithelial new growths of the liver into adenomas and carcinomas might be frowned upon on the basis that all adenomas are either actually or potentially malignant and therefore should be diagnosed and treated as carcinomas, although it is recognized that benign adenomas have been successfully enucleated.

A gross classification of these tumors is probably unimportant, inasmuch as the fundamental type in all might be the same, the physical characteristics only being different. Ewing's[9] nomenclature (dividing hepatomas into (1) solitary adenomas or hepatomas, (2) massive and (3) multiple carcinomas or hepatomas and (4) carcinomatous cirrhosis), is as useful as any and furnishes us with gross descriptive terms.

The controversy regarding the unicentric or multicentric origin of these tumors will probably not be settled for some time. Karsner, Winternitz, Ribbert and others have favored the unicentric origin. Van Heukelom,[15] Travis,[26] Counseller and McIndoe and others believed that they demonstrated that the origin may be multicentric. It is argued by the latter that in their case dissemination could never have been explained by thrombosis and embolism of the portal or hepatic vessels unless the emboli traveled against the blood or lymph flow which they term improbable. However, in one of my cases there was a large secondary mass in the spleen which makes one think of retrograde extension through the portal and splenic veins. This point, however, has very little practical importance.

The frequency of cirrhosis as an associated lesion and its rôle as an etiological factor is of considerable importance. It is the general impression by nearly everyone who has written on this

subject that there is an incidence of cirrhosis in hepatomas of from 70 to 100 per cent and in cholangiomas of from 40 to 60 per cent. The majority believe that the cirrhosis precedes and influences the development of carcinoma while a few believe that the cirrhosis is secondary. Counseller and McIndoe and Blumenau[3] believed primary carcinoma of the liver is a complication of cirrhosis in 3.9 per cent of 127 cases and 3.5 per cent of 198 cases respectively It would seem reasonable to expect to find it most frequently associated with cholangioma regardless of whether it were secondary or primary because we are familiar with bile duct proliferation in cirrhosis and periductal fibrosis is a common occurrence. There are still others who believe that the same stimulating factor is common for both cirrhosis and carcinoma. It is rather interesting that in this series of six hepatomas and two cholangiomas cirrhosis was found only once and that was associated with a hepatoma. In one other hepatoma there was an abundant hyaline stroma but nothing simulating cirrhosis.

The part played by chronic hepatic disease such as parasitic infections and toxic liver damage as the cause of primary carcinoma is striking. The cases of Pirie, Strong and Pitts and Smith occurring in Chinese, South Africians, and Philippinos strongly suggest the importance of chronic hepatic disease as an etiological factor. Ascoli stated that all of his patients gave a history of syphilis, malaria or alcoholism. In this hospital the incidence of primary carcinoma of the liver is not unusual and yet the prevalence of syphilis and alcoholism is far above the average; in spite of the large population of chronic alcoholics portal cirrhosis is an uncommon lesion encountered in our autopsies. The patients of this series were all white except one case (negro) of cholangioma and all males except one case of hepatoma. In some of these cases there was an outstanding alcoholic history but in other cases the history was indefinite.

An attempt was made to find out if there was any distinctive microscopical picture which could be relied upon in diagnosing these tumors. Cholangiomas were easily recognized in these two cases because they presented a fairly uniform microscopical picture. The cell morphology of hepatomas is variable and yet

there was a fairly characteristic architecture of these tumors with cord arrangement of cells and a vascularity which simulated or imitated normal sinusoids. Differentiation into bile ducts should probably be looked upon with suspicion. In many of these lesions differentiation is sufficiently complete to produce cells and a cell pattern so closely resembling normal hepatic parenchyma as to be quite unmistakable. Such a picture obtains in the so-called adenomas. In other instances differentiation is apparently poor and atypical patterns are produced; in such cases a positive diagnosis of primary carcinoma of the liver could hardly be made without a complete autopsy.

Two cases of metastatic melanoma of the liver are described both of which might have been considered primary in the liver and are no doubt as much primary as most of those previously reported. In one case there was an old injury to one eye to which no clinical suspicion of malignancy was attached. This eye was removed and sectioned more or less as an afterthought and might easily have been omitted in a routine autopsy and the primary site left undiscovered. In the other case no primary lesion was demonstrable but the history of the removal of a mole one year before is probably significant.

While metastasis to any organ is possible, the new growth process may remain confined to the liver and when extrahepatic involvement occurs, the lungs and the mediastinal and upper abdominal lymph nodes are the principle sites of secondary deposits. Of the latter there are several possibilities. In the six hepatomas here considered, there was metastasis to the upper abdominal lymph nodes in four instances, lungs and pancreas each twice, and the spleen and mediastinal nodes each once. Of the two cholangiomas there was no metastasis in one case and a secondary lesion only in the right auricle in the other. This experience, however, does not follow Ewing's statement that "extrahepatic metastases are much earlier and more frequent in biliary cancer than with hepatoma." In two of the cases in this series the capsule of the pancreas was quite extensively involved and the lymphatics of the pancreas were distended by new growth

masses. It is to be remembered in this connection that considerable lymphatic drainage from both the liver and pancreas goes to the coeliac nodes and from here retrograde dissemination of a hepatoma to the pancreas could occur. The peritoneum of the upper abdomen is frequently involved probably due to direct extension from involved lymph nodes.

CONCLUSIONS

(1) Eight cases of primary carcinoma of the liver were encountered in 1087 consecutive autopsies representing an incidence of 0.74 per cent.

(2) Six of these tumors were hepatomas and two cholangiomas.

(3) The patients were the type usually encountered in a charity hospital in any large city. Alcoholism and syphilis appear to play a minor etiological rôle.

(4) Cirrhosis was associated with only one of these cases (a hepatoma), yet no attempt is here made to dispute the reported relationship between cirrhosis and primary carcinoma of the liver in the experience of others.

(5) The two cases of secondary melanoma of the liver illustrate that probably most primary melanomas of the liver which have been reported are only apparently primary there.

(6) Diagnoses of primary sarcoma of the liver should probably be viewed with suspicion on the ground that many so diagnosed are of epithelial origin.

(7) A much higher percentage of primary carcinoma of the liver is apparently found in autopsies on patients in whom chronic hepatic diseases are prevalent.

(8) The gross appearance of hepatomas is not especially helpful in identifying the lesion but the histopathological picture is fairly distinctive and positive microscopical diagnosis can usually be made.

Acknowledgment and appreciation are extended to Dr. John M. Appel for his valuable services in reviewing the literature and in partially assembling this material.

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DISCUSSION

DR. I. DAVIDSOHN: The striking feature of Dr. Brines' report is the infrequency of cirrhosis in his cases of primary carcinoma of the liver which is as he himself emphasized, in such a sharp contrast to the prevalent opinions in the literature. In this connection it may be of interest that the question has not been settled as to whether the cirrhosis of the liver procedes or follows the development of the malignant process.

OBSERVATIONS MADE DURING A STUDY OF THE CYTOLOGY OF ENDOMETRIUM*

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During a study of the cytology of the endometrium in more than 100 fresh specimens obtained at operation, together with an equal number of specimens obtained from the pathologic museum, certain observations were made. Some of these are summarized in this paper.

The appearance of fresh tissues prepared by the freezing method and examined immediately was definitely different from that of the tissue in fixed sections. The shrinkage in fixed specimens was roughly 10 per cent of the nuclear diameter. The shrinkage from evaporation, exudation, and contraction of the tissue elements in specimens removed at operation was marked during the first hour after their removal. This shrinkage necessarily led to considerable distortion and to other artefacts. It was apparent that cells varied considerably in size and shape depending on their situation and that they moved far more than has generally been thought.

The mucosa appeared to vary between 1 and 5 mm. in diameter and there was no distinct division into layers. Each millimeter of added thickness corresponded roughly with one postmenstrual week. The stroma (fig. 1) consisted of a fine, loose network including blood vessels, lymph tracts, reticulo-endothelial cells, lymphocytes, and an occasional lymph follicle. The cervix differed in that the glands were of the racemose type and definitely

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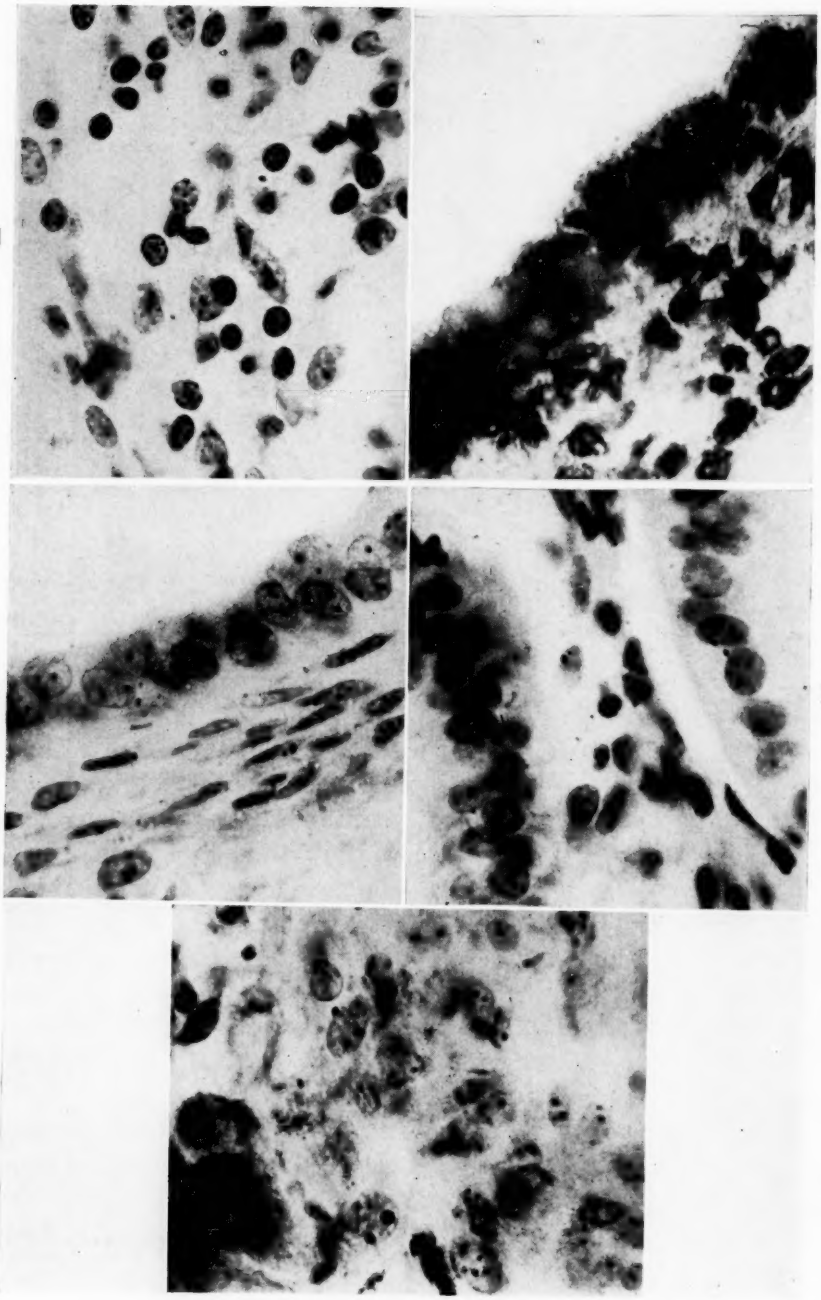

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 1. STROMA CELLS (× 600)
FIG. 2. CILIA ON ENDOMETRIUM (× 600)
FIG. 3. SECONDARY CYTOPLASIA (× 600)
FIG. 4. REGENERATION CELLS (× 600)
FIG. 5. MALIGNANT CELLS (× 600)

mucus-forming, with the stroma containing much more fibrous connective tissue. The cells of the endometrium varied with age, menstrual phase, pregnancy, ovarian changes, luteal reactions, infections, the presence or absence of neoplasms and probably in the presence of abnormal conditions of the thyroid, pituitary, suprarenal, or mammary glands. There was a continual change going on and regeneration following menstruation was very rapid.

Fetal endometrium[1] which forms at about the twelfth intrauterine week, presented a rather homogeneous structure. The stroma was densely filled with cells resembling early fibroblasts or histocytes. These might be referred to as histoblasts.

In premenstrual endometrium there was underdevelopment of the whole structure, although this was less marked in the cervix. Cilia (fig. 2) were seen in twelve of the fresh specimens, without any particular search, and in these cases there appeared to be, from the history, some association with infection.

Adult endometrium was fully developed. There was marked variation in individuals, depending principally on the menstrual cycle, unless neoplasm was present. The cells concerned were chiefly the histoblasts present in the stroma, which, as elsewhere in the body, form the chief elements of repair. They are early embryonic types of pleomorphic cells. They appear to be closely related to the monocytes. These cells were fully studied by Maximow.[3] I have observed them undergoing transformation from connective tissue elements into smooth muscle cells in the uterus of the rabbit. They are present in all connective tissue throughout the body; for instance, that in the spleen, bone marrow, sinusoids of the liver, lymph nodes and mucosa and surrounding smaller blood vessels; moreover, they are found in the omentum,[4] where they form, becoming more or less fixed lymph channels which, under abnormal conditions, develop into lymphatic channels of adult endothelium. From this cell, I believe, develop the several varieties of giant cells, the epithelioid cells, the Kupffer cells, the dust cells, the heart failure cells, the cholesterol macrophages, the decidual cells, the elements of the corpus luteum, the fat cells, and the pigment cells. These cells, apparently, are most important in immunity reactions and in infections.

That they are the cells concerned in malignancy has yet to be proved but it seems that they constitute the "repair" cells (regeneration cells), which are seen in neoplasms in the indefinite zone between the regions of benignancy and malignancy. One cannot help but feel that these cells appear to take on malignant characteristics.

A peculiar structure was encountered, which, under low magnification, might be taken for a lymph follicle, but under higher magnification there appeared a concentric arrangement of two types of stroma cells, greatly hypertrophied. There were changes in the surrounding stroma and glands. Another similar structure was seen adjacent, and in several instances the cells were undergoing change on one side of a gland similar to that seen at the border of malignant growths in the stomach and colon. The specimen was from a nullipara, fifty-one years of age. The history was that until eight months before operation menstruation always had been regular. Then menorrhagia and metorrhagia had appeared. There was a history of malignancy in the family. The pathologic diagnosis was multiple fibromyoma, hypertrophic endometrium, and chronic cystic cervicitis. The possibility of a decidual reaction had to be considered, but it was remarkable that a similar structure was present in several other cases in which the diagnosis was carcinoma, and in which two types of similar cells could be seen replacing glands. In one case this formation was present on the surface.

Postmenstrual endometrium presented evidence of diffuse abiotrophy with more or less marked sclerosis.

Pregnancy normally caused diffuse hypertrophy and hyperplasia of the histoblasts, forming decidual cells. There were specimens from the abnormal condition, hydatidiform mole, with its occasionally resulting malignant conditions, chorio-epithelioma.

Infection in the endometrium is particularly well guarded against, especially in the cervix, and judging from the results of some experiments done on animals, it would appear that there is a quick cytologic response to infection, with active outpouring of lymph and of phagocytic cells. Moreover, a wonderful internal barrier of defense cells is soon set up. Menstruation throws out much infection, which usually is superficial.

There seemed to be a definite relationship between neoplasms and hypertrophy and hyperplasia. This was evident in polyps, adenomas and carcinomas, and in fibromas, myomas and sarcomas. It was also evident in the most malignant types, in which carcinoma and sarcoma were indistinguishable. That we have been overwhelmed by classifications is evident when, to describe certain arrangements of tissue, the term "sarcomatous-carcinoma" is used without hesitation. The common condition "fibro-adenoma" is well known.

All the usual types of malignancy were seen in the endometrium. MacCarty's[5] primary, secondary and tertiary cytoplasia were demonstrated, and Broders' system of grading[2] could be applied as well here as elsewhere.

There was no sharp dividing line between a benign and a malignant condition, The so-called regenerative cells (figs. 3 and 4) were potentially malignant (fig. 5), and were pleomorphic.

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CAPILLARY WEAKNESS IN BACTERIAL ASTHMA*

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This discussion is concerned with twenty-three patients with asthma in whom a specific allergin was not demonstrated by the scratch tests, nor did the history and trial elimination give any clue as to a specific offender. Of 1074 patients with asthma classified by Rackemann[29] 61 per cent belonged to the groups designated "intrinsic" and "unclassified" showing the prevalence of these types while only 39 per cent was "extrinsic" in nature. I would regard my twenty-three patients as "intrinsic" asthmatics and further would divide the cases into the following subgroups: four, bacterial asthma of children; thirteen, bacterial asthma of adults, and six, reflex asthma, nose and throat only.

ONSET

Because of the confusion which results from the various explanations of this symptom complex, I constantly keep before my mind that the condition represents an impairment of health, a weakened physical condition. Each child began to have his asthma before the age of two years and without having had any recognized infectious disease, although in each there was the history of coryza preceding every spell of asthma. In three of the patients one parent or grandparent had suffered from the disorder. Cooke, Flood and Coca[6] showed that inheritance exerts a definite effect on the age at which symptoms appear and Kahn[19] believed that there is a hereditary factor in all patients with asthma. One can inherit abnormal tissue reactions and suffer asthma as a result even with a good constitution. On the other hand, one may begin life poorly constructed because of a toxic

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mother who supplied poor material for development in utero. This was demonstrated in a child who had rickets at birth, who had a pigeon breast, and whose lower ribs were depressed reducing the capacity and flexibility of the chest to a great extent.

The most impressive fact of the adult bacterial group is that in eleven of the thirteen, the onset began during, or shortly after, a severe infectious disease, pneumonia in seven, and influenza, of 1918 or 1919, in four. In another patient the onset occurred after the birth of three children within three years, but in the remaining patient there was not a definite association with any physical strain. The average age at onset was twenty-five years, the youngest was twelve and the oldest forty-eight. There was a family history of asthma in only one, a man whose asthma began after pneumonia at the age of thirty-four. The patients of this group originally had good constitutions but they had been injured by two or three infectious diseases as measles with or without serious pulmonary involvement, scarlet fever, diphtheria, whooping cough, rheumatism; probably the usual percentage had primary tuberculous infections and then came another severe strain such as pneumonia, influenza, or repeated pregnancies.

Patients in the group having nasal polypi began to have their symptoms at a later age, the average for six patients was fifty-one years but the onset was not closely associated with any particular disorder. However, these patients have had the diseases of childhood and numerous other infectious ailments. Throughout life they have persecuted their bodies by loss of sleep, by eating poor food or too much food, by excessive use of tobacco and alcoholic drinks, by overwork or too little work, by anxiety, by worry, by trouble, and by the stress and strain of living. With these habits of dissipation are often associated the focal infections, or perhaps the latter are the results of the former.

ALLERGY

There is some change in the tissue reactions of an asthmatic patient which makes his respiratory organs respond to various foreign substances and stimuli; there is sufficient experimental evidence to show that both the body cells and the blood partici-

pate in these reactions although the explanation is theoretical and the actual state of affairs has not been demonstrated. The reactions in the lungs which are of chief concern are the contraction of bronchial muscle and the inflammatory changes of the mucosa with congestion, vasomotor weakness with extreme relaxation of the vessels followed by extravasation of serum and cells, especially eosinophils, into the tissue, and there is still a debate as to which is more important. Manwaring[25] believed that increased specific capillary permeability will be shown to be the dominant fundamental physiologic change in protein sensitization to which all other anaphylactic reactions are secondary. Work on man and animals has demonstrated the highly specific nature of the allergic reaction but the inflammatory state of the respiratory tissue in asthma can be produced by so many factors that the specific allergic reaction does not explain the whole picture. The inflammatory state responsible for at least a portion of the asthmatic syndrome may be the residue of an acute respiratory infection.

THE MUCOSA OF THE RESPIRATORY TRACT IN ASTHMA

I have never examined the nose of an asthmatic patient during the symptomatic stage without finding it boggy, swollen, and wet. Nasal polypi represent collections of fluid with slight, fibrous stroma infiltrated with eosinophils, lymphocytes, and plasma cells; the same microscopic appearance is seen in the thickened scrapings of sinuses and in polypoid nasal mucosa. Portions of nasal epithelium obtained at autopsy by Kountz and Alexander[21] showed prominent glands undergoing mucoid degenerations, hyperplasia of the epithelium, edema, congestion, and thickening of the submucosal layer with cellular infiltration. In cases examined bronchoscopically during paroxysms, Clerf[5] found marked swelling and turgescence of the mucosa which appeared cyanotic and purple rather than red. In practically every case there was an increase in the quantity of secretion; this varied considerably. With suppuration the secretion was purulent, without odor, and could be traced to definite branches usually those of the lower lobes. In a larger group of cases, the secretion

mucoid in character, was found adherent to the mucosa of the trachea and bronchi. It often practically occluded the orifices of the smaller bronchial subdivisions. Owing to the tenacious character, great difficulty was experienced in its removal either with swabs or by a specimen collector. Objective evidence of spasm of the bronchi or trachea was not found in the cases examined. Jackson[18] found pulmonary secretions to cause partial or complete block of smaller bronchi by their valve-like action, and in many cases of asthma the air hunger seemed to be due to pumping out of air from both lungs. Bronchoscopic removal of the secretions that were acting as check valves almost always cured the air hunger. Autopsy reports are few but the findings as described by Rackemann,[28] Huber and Koessler,[17] Kountz and Alexander, and Bergstrand[3] were fairly uniform. The epithelial and sub-epithelial layers of the bronchi were essentially similar to those of the nasal mucous membranes. The goblet cells and bronchial glands seemed to have a conspicuous part in the process. There was intense congestion, some edema and cellular infiltration, the muscle layer of the 3 to 6 mm. bronchi was thickened while the walls were thinner and relatively more dilated in the 2 to 3 mm. bronchi; this latter finding gave support to the theory of muscle spasm as a cause for asthma. The lumen contained exudate of serum, mucus, and cells of varying degree, some of the small bronchi were so filled with exudate that the lumen was occluded completely. The parenchyma of the lung showed congestion and edema, emphysema, cellular infiltration, especially eosinophils, and some alveoli were filled with coagulated secretion.

RELATION OF ENDOCRINE GLANDS

Injections of adrenalin have always given remarkable relief in paroxysms of asthma and the relief is proportional to the degree of shrinkage of the mucosa, apparently restoring the vascular tone. I am not prepared to say how extensive is this shrinkage or whether it extends over the entire respiratory tract. I injected lipiodol into the maxillary sinus of one patient and found marked thickening of the mucosa. The patient was given 0.6 cc. of

adrenalin subcutaneously; twenty minutes later another roentgenogram was made but there was no change in the thickness of the mucosa. However, I do know that such shrinkage occurs in the mucosa of the nose and throat. The action of adrenalin is sympatho-mimetic and there is some reason to believe that the injection of adrenalin may stimulate the suprarenal glands to secretion through its acting on the sympathetic terminations in the glands, but this has not been conclusively established. I have personally experienced the effects of an intravenous injection of 0.5 cc. of adrenalin; the significant reaction is a painful, throbbing sensation over each kidney and in the head, with an expansile sensation in the head, this is accompanied by intense nervousness and rapid forceful heart action.

Vascular tone has been associated with the secretions of the adrenal medulla and the posterior lobe of the pituitary, but there are no data to appraise the importance of adrenalin and vasopressin in maintaining arterial tone. Although evidence was far from complete, Dale[9] thought a really important function of these harmones in relation to the normal circulation may be found in their power to check and to restrict within physiological limits the depressor effects of substances dilating the small vessels when they escape into the circulation. Probably the most acceptable function of the adrenal medulla constitutes Cannon's "emergency theory" whereby it is fitted for temporary reinforcement, during emergencies, of the effects of true sympathetic nerves on almost all organs supplied by them, especially on the circulation. Kellaway and Cowell[20] reported prompt acceleration of adrenalin output in the cat when a small dose of histamine was injected intravenously; the effects were slight and evanescent due to the balanced antagonism as compared with the grave and prolonged depressor effects of the same small dose of histamine in a cat deprived of the suprarenal medulla. This functional antagonism of adrenalin and histamine may give another and more direct hint to their functional importance. Hoskins[16] concluded that the collapse of the circulatory mechanism following adrenalectomy is proof of a definite functional interrelationship and Coomb's[7] experiments led her to believe that some product of the

adrenal tissue, medullary or cortical, is necessary for maintaining normal sympathetic nerve activities on the blood vessels.

The pituitary vasomotor principle, vasopressin, has a more prolonged action upon the vessels when injected, increasing the tone of the minute vessels without any discrimination corresponding to their nerve supply. Krogh[22] working with frogs presented evidence that led him to the conclusion that the pituitary vasoconstrictor has the function of maintaining the normal tone of the capillaries and therewith the normal restricted permeability of their walls. On the other hand there is no evidence that a recognizable loss of capillary tone follows removal of the posterior pituitary lobe in mammals. Dale suggests that vasopressin is another safeguard against circulatory collapse by a general and undiscriminating maintenance of tone in the small blood vessels when sympathetic impulses and adrenalin alike begin to fail under the stress of a prolonged and excessive demand for their action. He also offered very strongly suggestive evidence to show that adrenalin and vasopressin can restore tone after its loss by destruction of the nerve supply.

The medullo-adrenal secretion is taking second place in importance to that of the cortex since recent work has shown the really vital function of the cortex. Some uncertain observations associated the adrenal cortex with respiratory movements. It has been confirmed experimentally by Menten and Crile[27] and by Menten[26] who found that adrenalin endowed venous blood with the power to become converted into arterial blood and enable hemoglobin to become changed to oxyhemoglobin. Various symptoms observed in bilateral adrenalectomized animals are analagous to conditions often encountered in asthma. These animals very early show decreased arterial pressure, metabolism is disturbed, anorexia and gastro-intestinal disturbances occur and are followed by asthenia. The total work done by adrenalectomized rats before complete fatigue sets in was shown to be only one-sixteenth of that carried out by control animals. Many authors have shown that adrenalectomized animals are particularly sensitive to cold and various toxins, as morphine, nicotine, acetonitrile, histamine, and diphtheritic toxin. The effects on

the gastro-intestinal system were severe; Stewart and Rogoff[31] emphasized the frequent occurrence of gastric ulcer, Alverez[1] and associates found marked functional derangements. Banting and Gairns[2] demonstrated extensive pancreatic degeneration of longer lived dogs. Britton[4] found the pancreas of adrenalectomized marmots which lasted throughout the winter and perished in the spring to show extreme disturbance; usually the gland was very shrunken, thin and congested in appearance; on section it showed hemorrhagic patches, diffuse sclerosis and atrophy. Since severe disturbances of the digestive system is evident following adrenal removal, it is fair to assume that similar conditions are present in many toxic and infectious diseases. It is entirely possible that some of the digestive disorders in asthma have such an adrenal basis. Rowe[30] stated that skin reactions are negative in about 50 per cent of patients with food allergy. The deleterious effects of infectious disease on the adrenals was clearly shown by Elliott in autopsy specimens. According to Crowden[8] the application of external cold produces exhaustion of the adrenalin store of the suprarenal glands of cats provided a marked fall in body temperature occurs and persists. The vital function of the adrenal suffers with the general health as a result of the evil influences of bad habits of living and infectious disease. Think of the severe shock to the adrenal of a boy when he becomes sick from his first smoke or chew of tobacco and assign a proportional blow from each similar offense when the habit continues over a period of years. The effects of poor food were shown by Weil[32] in the statement that pellagra, a disease of persons obtaining much of their protein from maize of which the chief protein, zein, lacks tryptophan and lysin, greatly resembles Addison's disease. Also an increase of the cortex at the expense of the medullary portion of the adrenal was found in pigeons with an experimental avitaminosis produced by feeding them exclusively with polished rice.

OTHER FACTORS IN RESPIRATORY INFECTIONS

The specific allergic reaction has not been so definitely established in cases of bacterial asthma and the dyspnea often results

from the local irritation due to non-specific chemical or physical irritants introduced in large dosage. Other factors may produce an inflammatory state of the mucosa, making it more sensitive; thereby responding to non-specific irritants introduced in smaller dosage; and dyspnea may result from the mucosal swelling alone.

It is widely recognized that existing asthmatic states are made worse, or fresh attacks frequently precipitated, by fatigue. Holman[15] believed that allergy in the cell is in many ways analogous to the familiar fatigue phenomenon in which an individual at a certain stage of tiredness is hyperactive, highly irritable and often does more harm than good to himself and his associates. The fundamental conception is concerned with reactions of cells to various stimuli including those which arise from the presence of microbes. Such stimuli often demand reactions in cells with other specialized function and the failure to respond adequately may be due to many factors such as previous overactivity or underactivity, interference with blood supply, faulty diet, and similar general nutritional deficiencies. Normally, the cells of the body are resistant to bacterial infection and the failure in this resistance is in many cases simply a failure to react—a fatigue in the normal defence mechanism.

The "common cold" which so often follows slight exposure; even such trivial things as taking a bath or washing the hair under favorable circumstances, and which contributes so much to the frequency of exacerbations in asthma was discussed by Holman[14]. He believed the "cold" is a question involving a consideration of the factors influencing the circulatory mechanism. A capillary system capable of adapting itself to such emergencies will undoubtedly usually prevent such infections. Disturbances of the capillaries may result from variations of atmospheric heat and cold, humidity, changes in the composition of the blood, heat regulation and the dangers of excessive water intake, and reflex effects. These facts partially explain such clinical findings as the dyspnea from increased pulmonary ventilation due to poor evaporation and radiation from the skin, and the deleterious effects sometimes observed in excessive water intake and at times a slight improvement in the asthmatic state resulting from a restriction of fluids.

Some other conditions favoring the infecting organism are Vitamine A deficiency; edema and hydration which develop under restricted protein and a high carbohydrate diet, mild acidosis; lack of beneficial tonic effects of regulated exercise, general fatigue, constipation, worry, loss of sleep, and similar strains.

Coexistent sinus disease has been shown to be of tremendous significance in asthma.

Aside from the purely allergic reaction, excessive ingestion of food with fermentation and putrefaction is so closely related to so many asthmatic seizures that there must be some chemical or toxic basis for this association. The chemical reactions of the body are entirely dependent upon the food intake and a temporary alteration of tissue pH may follow the production of organic and inorganic acids in the bowel. Fisher[13] demonstrated the increased imbibition of hydrophyl colloids produced by variation in pH. MacLeod[24] showed that changes in tissue pH may occur without any change in the pH of the blood stream. The action of histamine, a putrefaction product, upon the capillaries is sufficient to cause local edema and Eustis[11,12] observed clinical asthma and urticaria resulting from amines of intestinal origin. McCarrison[23] felt that the functional perfection of the adrenal glands is dependent upon the balance of the food and upon the quality and quantity of its vitamines.

Sooner or later the individual develops a neurosis whereby he has a greater number of attacks because of the constant fear of the attack coming at an inconvenient time or of the embarassment that might result; or of the pity and solicitations of his associates. Then too the asthmatic patient at times employes his condition as an excuse to avoid obligations and duties of various types.

THERAPEUTICS

In the treatment of attacks, I have given these patients sufficient adrenalin to afford complete relief. Each patient was taught to give himself a hypodermic injection and this was of particular value because the patient himself could relieve attacks during the night and avoid loss of sleep. Atropine has been of

great value in the management of "colds." Each patient was instructed to use this drug as soon as the first sign of a "cold" appeared.

Prevention of attacks was attempted by control of the precipitating factors which included necessary surgery for sinus disease and very fortunately proper nasal surgery often gave temporary relief. Since both the secretions of the adrenal prevent nervous and muscle fatigue which predispose to asthma; since the cortico-adrenal secretion is so important in maintaining proper digestive function and since adrenalin remains the best measure in relieving asthma, it is fair to assume that the proper function of the adrenal is a necessary aim. It was demonstrated by Crowden and by Edmunds and Smith[10] that rest restored adrenalin to a depleted medulla and the latter workers showed also the depleting effect of stimulating drugs. Crowden's experiments showed also that food prevented adrenal exhaustion by cold. Abundance of rest and careful administration of good food over a long period of time improved the body structure of all these patients so that bouts of asthma were fewer and less severe although the asthma did not disappear completely in any patient. The restricted mode of living is not a great difficulty to the patient, but a more vexing problem is to adapt the occupation to the patient's capacity. Dehydration of the nose by argyrol tampons was frequently used with some success. Dehydration of pulmonary tissue by marked reduction of fluid intake was employed in two patients with some temporary relief of symptoms, but this procedure alone was not sufficient to produce noticeable relief.

SUMMARY

In the causation of bacterial asthma one should remember the possibility of injury to the endocrine glands, especially the adrenals. Factors which cause capillary weakness often precipitate attacks of asthma because of turgescence of pulmonary vessels. Therapeutic measures designed to restore the function of the adrenal glands were beneficial but not curative to my patients with bacterial asthma.

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NOTES ON TECHNIC

A Note on the Adaptation of Formalin-fixed Tissue for Mallory's and Weigert's Staining Methods

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Pathologists are constantly endeavoring to modify existing cytologic staining methods in an attempt to improve or simplify present technic, or else to introduce new methods for the better demonstration of cell structures. In a previous note* I described an adaptation to formalin-fixed material for Mallory's stains, and since that time an even more satisfactory modification has been adopted in our laboratory.

The formalin-fixed material is washed briefly in running water or ammonia water,[1] although both these procedures may be omitted. If there is much blood in the tissue, the ammonia water reduces the formalin precipitate on the stained preparations. The tissue is fixed in Zenker's solution for six to eight hours, and washed in running water for twenty minutes to half an hour. The tissue is placed overnight or longer in Weigert's secondary mordant for myelin sheath stains.[2] It is then embedded in paraffin and cut and stained in the usual way with any of Mallory's

* Kernohan, J. W.: A new modification of Mallory-Heidenhain's differential staining method and adaptation of formalin-fixed material for Mallory's stains. Am. Jour. Clin. Path., **1:** 399–403. 1931.

[1] Ammonia water is made by using 10 c.c. of tap water and adding approximately 60 drops of ammonia.

[2] Weigert's secondary mordant for myelin sheath stains:

Acetate of copper	5	gm.
Chromium fluoride	2.5	gm.
Acetic acid, 36 per cent	5	c.c.
Water	100	c.c.
Formalin	10	c.c.

stains. In the last year, I have used this method for peripheral nerves, spinal cord, and small pieces of brain tissue, and have found it equal to the original methods of Weigert. It gives as satisfactory results as the modification which I described previously, and it is also much more rapid, as it saves approximately four days in the procedure. The results obtained by this modification are superior to and more uniform than those obtained by treating sections of formalin-fixed material on a microscopic slide with Zenker's solution alone. It is equally valuable for all tissues of the body, and especially useful in studying the capillary loops and basement membrane of the glomeruli of the kidney by the Mallory-Heidenhain stain.

A Note on Direct Matching of Blood Prior to Transfusion

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(1) Draw a drop of blood from patient's finger tip to the 1 mark in a leukocyte counting pipette and follow with 5 per cent sodium citrate solution to the 11 mark.

(2) Mix thoroughly by shaking and transfer to small glass vial suitably marked for identification.

(3) Repeat for each donor.

(4) With an erythrocyte pipette, make a 9 to 1 combination of patient's and donor's blood by drawing blood from donor's vial to the first or 0.1 mark and patient's to the 1 mark at top of lower portion of the pipette.

(5) Transfer mixture to end of a glass slide and mix by alternate sucking and blowing three or four times. Add a small drop of saline and cover with cover slip.

(6) Now make a 1:1 dilution by drawing patient's blood from the vial to the 0.5 mark and donor's blood to the 1 mark. Mix and transfer to the other end of slide in same manner.

(7) Prepare a separate slide in this way for each donor. There is then a mixture of 9 parts of patient's blood to 1 of donor's at one end of slide and a 1 to 1 mixture at other end.

(8) Agglutination will show up both micro- and macroscopically in two or three minutes at room temperature.

(9) If no clumping occurs in fifteen minutes transfusion is safe.

(10) Transfusion is dangerous if agglutination is present in the 9 to 1 combination.

(11) If the 9 to 1 mixture is clear and the 1 to 1 shows agglutination, transfusion can be done but with caution; be ready to stop at once if untoward symptoms develop.

EDITORIAL

The Erythrocyte Sedimentation Test

We are indebted to Fahraeus for initiating observations on the sedimentation rate of erythrocytes when blood is mixed with anticoagulants and allowed to stand in tubes. Since his publication in 1918 a vast literature has accumulated. At first this dealt with methods and attempts at explaining the phenomenon, then with the test as applied to various diseases and more recently with critical analyses pointing out previous fallacies and setting up the limitations of usefulness of the test.

It is of course clear that the relation of the specific gravity and mass of the cell to the specific gravity of the plasma must determine the rate of fall but the factors influencing these reactions still remain obscure. To some the content of fibrinogen seems to be all important, to others the size of the cells, still others think the lipoid content of the serum is a factor. That the number of erythrocytes per unit of blood is of tremendous importance has been clearly shown by Gram, who made his correction in terms of hemoglobin content, by Meier and by Rourke and Ernstene on the basis of cell counts, and now more recently by Walton[1] who has clarified this consideration. He demonstrated a distinct relation between the rate of sedimentation and the number of erythrocytes showing that the rate increased as the number of erythrocytes decreased. This he observed experimentally by varying the concentration of cells with the addition or subtraction of the patient's own plasma. Further he has greatly simplified the procedure of performing the test and correcting for the number of erythrocytes.

Walton uses 3.8 per cent sodium citrate in a ratio of 1:10 with the blood. He advises a 6 mm. diameter tube and cautions that

[1] Walton, A. A. R.: The erythrocyte sedimentation test; a clinical and experimental study. Quart. Jour. Med. **2**: 79–115. 1933.

the tube must be held vertically and during the hour should be at a temperature between 19° and 23°C.

It is evidently important to correct the test for erythrocyte count since a difference of 1,000,000 cells will often double the rate, hence uncorrected rates will give false results.

Based on a 5,000,000 erythrocyte count, no normal person will have a rate higher than 5.5 mm., and as a rule females have a higher rate than males. Normal processes that affect the rate are the menstrual cycle and pregnancy.

The test has suffered adverse criticism chiefly due to the fact that the earlier workers tried to make a specific diagnostic test of this reaction and it did not take long to break down this thesis. Many discarded the test and it is only recently that due to a clearer understanding of its limitations it is gaining advocates.

The view is now taken that the stable condition of the blood, attained by the age of one year, is lessened in relation to the severity of pathological processes regardless of their causes and that illness of any nature increases the sedimentation rate. As one becomes more ill the rate increases. Further, the rate increases often before other signs are manifested. In this light the test becomes of great value in the prognosis of disease, in indicating latent infections and in many problems of differential diagnosis. In separating neurotic patients from patients suffering with organic diseases the test is of great value, and in following the cause of acute infectious diseases and convalescent surgical patients, valuable warnings may be received even several days ahead of clinical signs or a decreasing rate may remove unfounded fears.

This very simple test should be more widely used for it frequently gives a quick answer to a difficult problem.

T. B. MAGATH.

NEWS AND NOTICES

The Twelfth Annual Convention of the American Society of Clinical Pathologists

The Twelfth Annual Convention of the American Society of Clinical Pathologists will be held in Milwaukee June 9–12, with Headquarters at the Pfister Hotel. The Program Committee has planned an exceptionally fine program and it is hoped that it will be well attended. A particular feature is the Friday afternoon Symposium on "The Medico-Legal Postmortem" with the following subjects and speakers:

The Medico-Legal System of the United States. O. T. Schultz, Evanston, Illinois.

The Medico-Legal Autopsy. Charles Norris and A. V. St. George, New York City.

Postmortem Technic in Gunshot Wounds, Stabbing and Strangulation Cases. H. S. Martland, Newark, New Jersey.

Pathologic Anatomy in Cases of Drowning. E. L. Miloslavich, Milwaukee, Wisconsin.

The Rôle of Toxicology in a Medico-Legal Autopsy. A. O. Gettler, New York City.

Discussion. William D. McNally, Chicago, Illinois.

A Round Table Discussion dealing with the State Laboratories and laboratory technic will be held at the Pfister Hotel Friday June 9. The Annual Banquet will be Saturday evening and the Business Meeting on Monday.

Owing to the fact that the Century of Progress Exposition will be in full force the local committee has assumed that wives and children will accompany clinical pathologists, accordingly they have made arrangements for social features which will appeal to the family. This includes a boat trip on Lake Michigan on Sunday. Those who desire more information than was contained in the letter of April 11th, should get in touch with either the

members of the local committee or the chairman of the Program Committee.

Dr. Thomas Parran, Jr., Commissioner of Health, State of New York has just issued the new requirements for surgical pathologists in the State of New York laboratories. This follows the same general standards set up for directors and bacteriologists which include at least four years experience or training in the field subsequent to graduation. In addition to this, surgical pathologists are given a practical examination in the form of a series of tissue sections from which they must make diagnoses. The Public Health law establishing these conditions was based on the theory that numerous reports of tissue were being made by pathologists who lacked the proper qualifications and that this was a serious matter since such an error was likely to result either in a needless operation or in the failure to operate when the patient needed it.

Owing to the fact that so few abstracts of papers were submitted, it was decided to omit their publication in this issue of the JOURNAL.